Docket No. 245773US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Minoru SAKURAI, et al. GAU:

SERIAL NO: New Application EXAMINER:

FILED: Herewith

FOR: AMINOALCOHOL DERIVATIVES

REQUEST FOR PRIORITY

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

☐ Full benefit of the filing date of U.S. Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §120**.

☐ Full benefit of the filing date(s) of U.S. Provisional Application(s) is claimed pursuant to the provisions of **35 U.S.C. §119(e)**: **Application No.** **Date Filed**

■ Applicants claim any right to priority from any earlier filed applications to which they may be entitled pursuant to the provisions of **35 U.S.C. §119**, as noted below.

In the matter of the above-identified application for patent, notice is hereby given that the applicants claim as priority:

COUNTRY	APPLICATION NUMBER	MONTH/DAY/YEAR
Australia	2002952839	November 21, 2002

Certified copies of the corresponding Convention Application(s)

■ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

☐ were filed in prior application Serial No. filed

☐ were submitted to the International Bureau in PCT Application Number
Receipt of the certified copies by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

☐ (A) Application Serial No.(s) were filed in prior application Serial No. filed ; and

☐ (B) Application Serial No.(s)

- ☐ are submitted herewith
- ☐ will be submitted prior to payment of the Final Fee

Respectfully Submitted,

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Canberra

I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002952839 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 21 November 2002.

WITNESS my hand this
Tenth day of November 2003

J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Aminoalcohol Derivatives"

The invention is described in the following statement:

DESCRIPTION

AMINOALCOHOL DERIVATIVES

TECHNICAL FIELD

This invention relates to new aminoalcohol derivatives and salts thereof which are beta-3 (β_3) adrenergic receptor agonists and useful as a medicament.

DISCLOSURE OF INVENTION

This invention relates to new aminoalcohol derivatives which are β_3 adrenergic receptor agonists and salts thereof.

More particularly, it relates to new aminoalcohol derivatives and salts thereof which have gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence, anti-pollakiuria activities, anti-diabetes and anti-obesity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method of using the same therapeutically in the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in a human being or an animal.

One object of this invention is to provide new and useful aminoalcohol derivatives and salts thereof which have gut sympathomimetic, anti-ulcerous, lipolytic, anti-urinary incontinence, anti-pollakiuria activities, anti-diabetes and anti-obesity.

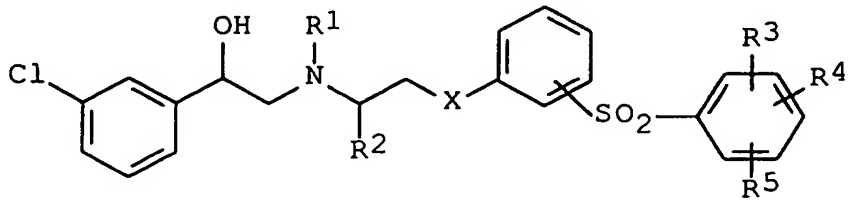
Another object of this invention is to provide processes for the preparation of said aminoalcohol derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said aminoacohol derivatives and salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention of aforesaid diseases in a human being or an animal, using said

aminoalcohol derivatives and salts thereof.

The object aminoalcohol derivatives of this invention are new and can be represented by compound of the following formula [I]:



[I]

wherein

X is bond, $-CH_2-$ or $-O-$,

R^1 is hydrogen or an amino protective group,

R^2 is hydrogen or lower alkyl,

R^3 is hydrogen or carboxy,

R^4 is hydrogen, halogen, hydroxy, lower alkyl of lower alkoxy, and

R^5 is hydrogen; halogen; hydroxy;

phenyl optionally substituted with carboxy or lower alkoxycarbonyl; lower alkoxy optionally substituted with carboxy or lower alkoxycarbonyl; lower alkyl optionally substituted with carboxy or lower alkoxycarbonyl; carboxy; lower alkoxycarbonyl; mono(or di or tri)halo(lower)alkylsulfonyloxy; phenoxy substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl; or pyridyloxy optionally substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl,

provided that when X is bond or $-CH_2-$, then

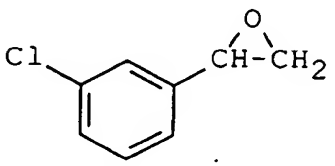
(1) R^5 is mono(or di or tri)halo(lower)-alkylsulfonyloxy; phenoxy substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl; or pyridyloxy optionally substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl, or

(2) R^4 is hydroxy, and R^5 is halogen; hydroxy; phenyl optionally substituted with carboxy or lower alkoxycarbonyl; lower alkoxy optionally substituted with carboxy or lower alkoxycarbonyl; lower alkyl optionally substituted with carboxy or lower alkoxycarbonyl; carboxy; or lower alkoxycarbonyl,

or a salt thereof.

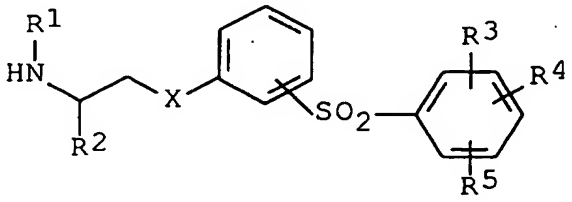
According to this invention, the object compounds can be prepared by processes which are illustrated in the following schemes.

Process 1

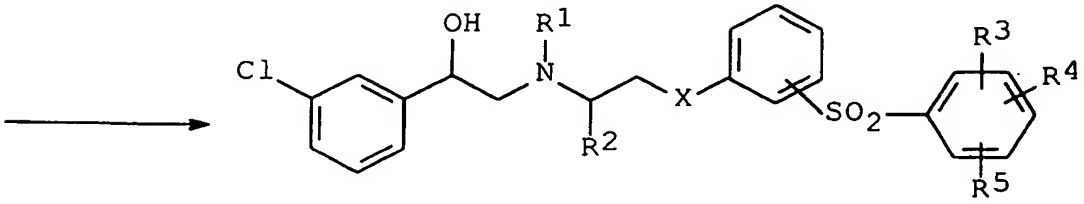


[II]

+

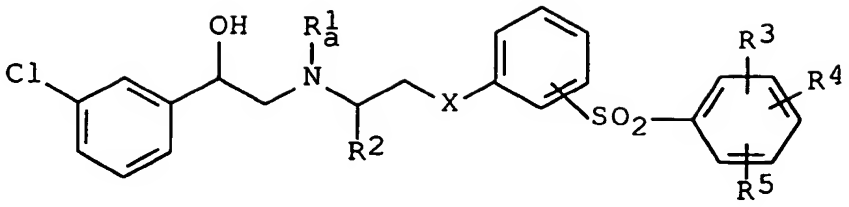


[III]
or a salt thereof



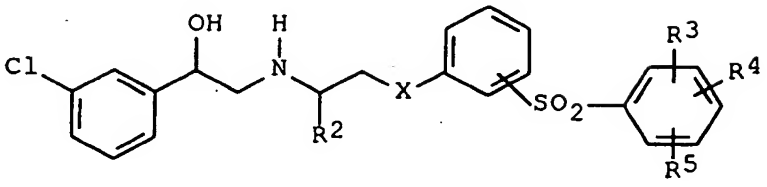
[I]
or a salt thereof

Process 2



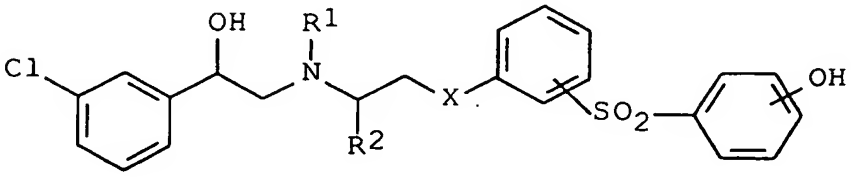
[Ia]
or a salt thereof

elimination reaction of the amino protective group



[Ib]
or a salt thereof

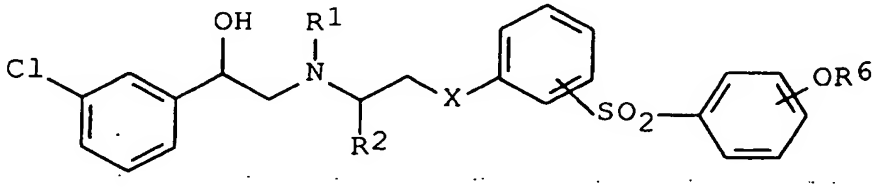
Process 3



+ Y-R6

[Ic]
or a salt thereof

[IV]
or a salt thereof



[Id]
or a salt thereof

wherein X, R^1, R^2, R^3, R^4 and R^5 are each as defined above,
R^1_a is an amino protective group, and
R^6 is lower alkyl optionally substituted with carboxy or lower alkoxycarbonyl; phenyl substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl; or pyridyl optionally substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl.

As to the starting compounds [II], [III], [Ia], [Ic] and [IV], some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or a conventional manner.

In the above and subsequent description of the present specification, suitable examples of the various definition to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" and "lower alkyl" moiety in the term of "mono(or di or tri)halo(lower)alkylsulfonyloxy" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-methylpentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like, in which more preferable one is C_1-C_4 alkyl, and the most preferable one is methyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the term of "lower alkoxycarbonyl" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, t-butoxy,

pentyloxy, t-pentyloxy, hexyloxy and the like, in which preferable one is C_1-C_4 alkoxy, and the most preferable one is methoxy or ethoxy.

Suitable "lower alkanoyl" may include formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl and the like, in which preferable one is C_2-C_4 alkanoyl, and the most preferable one is formyl.

Suitable "halogen" may be fluoro, chloro, bromo and iodo, in which preferable one is chloro.

Suitable "mono(or di or tri)halo(lower)-alkylsulfonyloxy" may include chloromethanesulfonyloxy, dichloromethanesulfonyloxy, trichloromethanesulfonyloxy, bromomethanesulfonyloxy, dibromomethanesulfonyloxy, tribromomethanesulfonyloxy, fluoromethanesulfonyloxy, difluoromethanesulfonyloxy, trifluoromethanesulfonyloxy, 1 or 2-chloroethanesulfonyloxy, 1 or 2-bromoethanesulfonyloxy, 1 or 2-fluoroethanesulfonyloxy, 1,1-difluoroethanesulfonyloxy, 2,2-difluoroethanesulfonyloxy and the like, in which more preferable one is mono(or di or tri)halo(C_1-C_4)alkylsulfonyloxy, and the most preferable one is trifluoromethanesulfonyloxy.

Suitable example of "amino protective group" moiety may be common amino protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxycarbonyl [e.g. tert-butoxycarbonyl, tert-amyloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl,

ar(lower)alkyl [e.g. trityl, benzyl, etc.], and the like, in which preferable one is benzyl or tert-butoxycarbonyl.

Suitable salts of the object aminoalcohol derivative [I] are pharmaceutically acceptable salts and include conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, oxalate, maleate, fumarate, tartrate, citrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc., an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

The Processes 1 to 3 for preparing the object compounds of the present invention are explained in detail in the following.

Process 1

The object compound [I] or a salt thereof can be prepared by reacting a compound [II] with a compound [III] or a salt thereof.

Suitable salt of the compound [III] may be the same as those exemplified for the compound [I].

The reaction is preferably carried out in the presence of a base such as an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkaline earth metal carbonate [e.g. magnesium carbonate, calcium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline or the like.

The reaction is usually carried out in a conventional solvent, such as an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], diethyl ether, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 2

The object compound [Ib] or a salt thereof can be prepared by subjecting a compound [Ia] or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compounds [Ia] and [Ib] may be the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 7 or 25 mentioned below.

Process 3

The object compound [Id] or a salt thereof can be prepared by reacting a compound [Ic] or a salt thereof with a compound [IV] or a salt thereof.

Suitable salts of the compounds [Ic] and [IV] may be the same as those exemplified for the compound [I].

This reaction can be carried out in a similar manner to that of Example 22 or 24.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like, and converted to the desired salt in conventional manners, if necessary.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

It is further to be noted that isomerization or rearrangement of the object compound [I] may occur due to the effect of the light, acid base or the like, and the compound obtained as the result of said isomerization or rearrangement if also included within the scope of the

present invention.

It is also to be noted that the solvating form of the compound [I] (e.g. hydrate, etc.) and any form of the crystal of the compound [I] are included within the scope of the present invention.

The object compound [I] or a salt thereof possesses gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities, and are useful for the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals, and more parcitularly for the treatment and/or prevention of spasm or hyperanakinesia in case of irritable bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis, cholecystopathy, cholantitis, urinary calculus and the like; for the treatment and/or prevention of ulcer such as gastric ulcer, duodenal ulcer, peptic ulcer, ulcer causes by non steroidal anti-inflammatory drags, or the like; for the treatment and/or prevention of dysuria such as pollakiuria, urinary incontinence or the like in case of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis, prostatic hypertrophy or the like; for the treatment and/or prevention of pancreatitis, obesity, diabetes, glycosuria, hyperlipidemia, hypertension, atherosclerosis, glaucoma, melancholia, depression or the like; for the treatment and/or prevention of diseases as the result of insulin resistance (e.g. hypertension, hyperinsulinemia, etc.); for the treatment and/or prevention of neurogenetic inflammation; and for reducing a wasting condition, and the like.

Additionally, β_3 adrenergic receptor agonists are known to lower triglyceride and cholesterol levels and to raise high density lipoprotein levels in mammals (US Patent No.

5,451,677). Accordingly, the object compound [I] in useful in the treatment and/or prevention of conditions such as hyper-triglyceridaemia, hypercholesterolaemia and in lowering high density lipoprotein levels as well as in the treatment of atherosclerotic and cardiovascular diseases and relates conditions.

Moreover, the object compound [I] is useful for inhibiting uterine contractions, preventing premature labor, and treating and preventing dysmenorrhea.

In order to show the usefulness of the compound [I] for the prophylactic and therapeutic treatment of above-mentioned disease in human being or animals, the pharmacological test data of a representative compound thereof are shown in the following.

Test

Effect on the increase in intravesical pressure induced by carbachol in anesthetized dog

Test Compound

(1) [[4-[[4-[(2R)-2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoyl]-(methyl)amino]acetic acid hydrochloride (the object compound of Example 25 mentioned below)

Test Method

Female Beagle dogs weighing 8.0-15.0 kg were fasted for 24 hours and maintained under halothane anesthesia. A 12F Foley catheter was lubricated with water soluble jelly, inserted into the urethral orifice and advanced approximately 10 cm until the balloon tip was placed well inside the bladder. The balloon was then inflated with 5 ml of room air and catheter slowly withdrawn just part the

first resistance that is felt at the bladder neck. Urine was completely drained out through the catheter, and 30 ml of biological saline was infused. The catheter was connected to pressure transducer, and intravesical pressure was continuously recorded. Intravenous administration of test compound (I) inhibited carbachol (1.8 μg/kg)-induced increase in intravesical pressure (IVP).

Test Results

Treatment	% inhibition of carbachol-induced increase in IVP
Test Compound (1) (0.032 mg/kg)	80.8%

Preferred embodiments of the object compound [I] are as follows:

X is bond, $-CH_2-$ or $-O-$,
R^1 is hydrogen,
R^2 is hydrogen or lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl),
R^3 is hydrogen,
R^4 is hydrogen, halogen (more preferably chloro), hydroxy, lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl) or lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy), and
R^5 is hydrogen; halogen (more preferably chloro); hydroxy; phenyl optionally substituted with carboxy or lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably methoxycarbonyl or ethoxycarbonyl); lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy) optionally substituted with carboxy or lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably ethoxycarbonyl); lower

alkyl (more preferably C_1-C_4 alkyl, most preferably methyl) optionally substituted with carboxy or lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably ethoxycarbonyl); carboxy; lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably ethoxycarbonyl); mono(or di or tri)halo(lower)alkylsulfonyloxy (more preferably mono(or di or tri)halo(C_1-C_4)alkylsulfonyloxy, most preferably trifluoromethanesulfonyloxy); phenoxy substituted with lower alkanoyl (more preferably C_1-C_4 alkanoyl, most preferably formyl), carboxy or lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably ethoxycarbonyl); or pyridyloxy optionally substituted with lower alkanoyl (more preferably C_1-C_4 alkanoyl, most preferably formyl), carboxy or lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably ethoxycarbonyl),

provided that when X is bond or $-CH_2-$, then

(1) R^5 is phenoxy substituted with lower alkanoyl (more preferably C_1-C_4 alkanoyl, most preferably formyl), carboxy or lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably ethoxycarbonyl), or

(2) R^4 is hydroxy, and R^5 is carboxy or lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably ethoxycarbonyl).

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

Under nitrogen, to a mixture of 2-phenylethanamine (40 g) and triethylamine (59.8 ml) in tetrahydrofuran (250 ml) was added trifluoromethanesulfonic anhydride (51.3 ml) dropwise under ice-water cooling, and the mixture was

stirred at the same temperature for 1 hour. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give 2,2,2-trifluoro-N-(2-phenylethyl)acetamide (67.73 g).

NMR ($CHCl_3$, δ): 2.89 (2H, t, J=7Hz), 3.64 (2H, q, J=7Hz), 7.20-7.40 (5H, m)

Preparation 2

The following compound was obtained according to a similar manner to that of Preparation 48.

(R)-[2-[(Trifluoroacetyl)amino]propyl]benzenesulfonyl chloride

NMR (DMSO-d_6, δ): 2.83 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 7.10-7.20 (2H, m), 7.40-7.60 (2H, m)

Preparation 3

Under nitrogen atmosphere, to a suspension of zinc powder (2.29 g) in 1,2-dichloroethane (10 ml) was added dichlorodimethylsilane (4.3 ml). The mixture was heated to 55°C whereupon a solution of 4-[2-[(trifluoroacetyl)amino]-ethyl]benzenesulfonyl chloride (3.15 g) and 1,3-dimethyl-2-imidazolidinone (3.3 ml) in 1,2-dichloroethane (10 ml) was added dropwise while keeping the temperature below 75°C. The mixture was stirred at 70°C for 1.5 hours and allowed to cool to room temperature. Methanol (5 ml) was added to the mixture and the mixture was stirred at room temperature for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give 2,2,2-trifluoro-N-[2-(4-

mercaptophenyl)ethyl]acetamide (1.48 g) as a white powder.

NMR ($CDCl_3$, δ): 2.84 (2H, t, J=7Hz), 3.44 (1H, s), 3.59 (2H, q, J=7Hz), 6.27 (1H, br s), 7.06 (2H, d, J=8Hz), 7.25 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 272 $(M+Na)^+$

Preparation 4

Under nitrogen at room temperature, to a solution of 2,2,2-trifluoro-N-[2-(4-mercaptophenyl)ethyl]acetamide (1.0 g) in N,N-dimethylformamide (20 ml) were added 4-chloro-2-pyridinecarboxylic acid (695 mg) and potassium carbonate (1.22 g), and the mixture was stirred at 100°C for 26 hours. The mixture was cooled to room temperature, and iodoethane (0.355 ml) was added. After being stirred at the same temperature for 12 hours, the resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3:1 to 1:2) to give ethyl 4-[[2-[2-[(trifluoroacetyl)amino]ethyl]-phenyl]thio]-2-pyridinecarboxylate (713 mg).

NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7.1Hz), 2.97 (2H, t, J=7.1Hz), 3.6-3.7 (2H, m), 4.43 (2H, q, J=7.1Hz), 7.0-7.05 (1H, m), 7.31 (2H, d, J=8.1Hz), 7.53 (2H, d, J=8.1Hz), 7.76 (1H, d, J=1.9Hz), 8.44 (1H, d, J=5.4Hz)

(+)ESI-MS (m/z): 399 $(M+H)^+$

Preparation 5

To a solution of ethyl 4-[[4-[2-[(trifluoroacetyl)-amino]ethyl]phenyl]thio]-2-pyridinecarboxylate (631 mg) in a mixture of ethanol (6.3 ml) and methanol (10 ml) was added 1N sodium hydroxide at room temperature, and the mixture was

stirred at the same temperature overnight. To the resulting mixture was added 1N hydrochloric acid (6.3 ml) and the mixture was evaporated under reduced pressure. Under nitrogen, the mixture of the obtained product and a reagent of 10-20% hydrogen chloride in methanol (20 ml) was refluxed for 24 hours. After evaporation, to a mixture of the residue in a mixture of tetrahydrofuran (5 ml) and water (5 ml) was added a solution of di-tert-butyl dicarbonate (691 mg) in tetrahydrofuran (3 ml) with adjusting pH to around 8 by 5N sodium hydroxide at room temperature. After being stirred at the same temperature for 1.5 hours, to the resulting mixture was added ethyl acetate followed by separation. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1:1 to 1:5) to give methyl 4-[[4-[2-[(tert-butoxycarbonyl)amino]-ethyl]phenyl]thio]-2-pyridinecarboxylate (470 mg).

NMR ($CDCl_3$, δ): 1.44 (9H, s), 2.87 (2H, t, J=7.0Hz), 3.35-3.5 (2H, m), 3.97 (3H, s), 7.0-7.05 (1H, m), 7.32 (2H, d, J=8.1Hz), 7.50 (2H, d, J=8.1Hz), 7.82 (1H, d, J=1.9Hz), 8.44 (1H, d, J=5.2Hz)

(+)ESI-MS (m/z): 411 $(M+Na)^+$

Preparation 6

Under nitrogen at 5°C, to a solution of methyl 4-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]thio]-2-pyridinecarboxylate (461 mg) in dichloromethane (10 ml) was added m-chloroperoxybenzoic acid (655 mg), and the mixture was stirred at room temperature for 3.5 hours. The resulting mixture was poured into aqueous sodium thiosulfate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate two times and brine, dried over anhydrous magnesium sulfate, evaporated under reduced

pressure and dried in vacuo to give methyl 4-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-2-pyridinecarboxylate (514 mg).

NMR ($CDCl_3$, δ): 1.39 (9H, s), 2.88 (2H, d, J=6.9Hz), 3.3-3.45 (2H, m), 4.04 (3H, s), 7.40 (2H, d, J=8.3Hz), 7.85-8.0 (3H, m), 8.54 (1H, m), 8.95 (1H, d, J=5.1Hs)

(+)ESI-MS (m/z): 443 $(M+Na)^+$

Preparation 7

Under nitrogen at room temperature, a solution of methyl 4-[[4-[2-[(tert-butoxycarbonyl)amino]ethyl]phenyl]-sulfonyl]-2-pyridinecarboxylate (500 mg) and hydrogen chloride (4N in ethyl acetate, 4 ml) in ethyl acetate (4 ml) was stirred for 3 hours. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and chloroform. After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give methyl 4-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-pyridinecarboxylte (346 mg).

NMR (DMSO-d_6, δ): 2.6-2.85 (4H, m), 3.8-3.9 (3H, m), 7.05-7.2 (2H, m), 7.35-7.5 (2H, m), 7.75-8.2 (3H, m)

(+)ESI-MS (m/z): 321 $(M+H)^+$

Preparation 8

The following compound was obtained according to a similar manner to that of Preparation 44.

N-[2-[4-[(3,4-Dihydroxyphenyl)sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide

NMR (DMSO-d_6, δ): 2.86 (2H, t, J=7.0Hz), 3.2-3.5 (2H, m), 6.89 (1H, d, J=8.4Hz), 7.2-7.3 (2H, m), 7.42

(2H, d, J=8.3Hz), 7.78 (2H, d, J=8.3Hz)

(+)ESI-MS (m/z): 412 $(M+Na)^+$

Preparation 9

Under nitrogen at 5°C, to a solution of N-[2-[4-[(3,4-dihydroxyphenyl)sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (8.68 g) in N,N-dimethylformamide (86 ml) were added potassium carbonate (3.39 g) and benzyl bromide (2.92 ml), and the mixture was stirred at room temperature for 36 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 4:3) to give N-[2-[4-[[4-(benzyloxy)-3-hydroxyphenyl]sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (4.38 g).

NMR ($CDCl_3$, δ): 2.93 (2H, t, J=7.1Hz), 3.5-3.7 (2H, m), 5.15 (2H, s), 6.95-7.1 (1H, m), 7.2-7.6 (9H, m), 7.8-7.9 (2H, m)

(+)ESI-MS (m/z): 502 $(M+Na)^+$

Preparation 10

Under nitrogen at 5°C, to a solution of N-[2-[4-[[4-(benzyloxy)-3-hydroxyphenyl]sulfonyl]phenyl]ethyl]-2,2,2-trifluoroacetamide (1.68 g) and 2,6-lutidine (0.527 ml) in dichloromethane (50 ml) was added trifluoromethanesulfonic anhydride (0.648 ml), and the mixture was stirred at the same temperature for 1 hour. The resulting mixture was poured into aqueous ammonia and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with 1N hydrochloric acid, water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure.

The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 4:3) to give 2-(benzyloxy)-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]phenyl trifluoromethanesulfonate (1.59 g).

NMR ($CDCl_3$, δ): 2.9-3.0 (2H, m), 3.55-3.7 (2H, m), 5.23 (2H, s), 7.15 (1H, d, J=8.7Hz), 7.3-7.45 (7H, m), 7.75-7.9 (4H, m)

(+)ESI-MS (m/z): 634 $(M+Na)^+$

Preparation 11

Under nitrogen at room temperature, to a solution of 2-(benzyloxy)-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]phenyl trifluoromethanesulfonate (1.58 g) in N,N-dimethylformamdie (12 ml) were added palladium(II) acetate (29 mg), 1,3-bis(diphenylphosphino)propane (53 mg), ethanol (6 ml) and triethylamine (1.08 ml), and under carbon monoxide (1 atm), the mixture was stirred at 60°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 4:3) to give ethyl 2-(benzyloxy)-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]benzoate (959 mg).

NMR ($CDCl_3$, δ): 1.34 (3H, t, J=7.1Hz), 2.85-3.0 (2H, m), 3.5-3.65 (2H, m), 4.37 (2H, q, J=7.1Hz), 5.22 (2H, s), 7.10 (1H, d, J=8.9Hz), 7.25-7.5 (5H, m), 7.85-7.9 (2H, m), 7.99 (1H, dd, J=2.5, 8.7Hz), 8.33 (1H, d, J=2.5Hz)

(+)ESI-MS (m/z): 558 $(M+Na)^+$

Preparation 12

Under nitrogen at 5°C, to a solution of ethyl 2-

(benzyloxy)-5-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]benzoate (957 mg) in N,N-dimethylformamide (15 ml) was added sodium hydride (60% in oil, 78.6 mg), and the mixture was stirred at room temperature for 30 minutes. The mixture was cooled to 5°C, and benzyl bromide (0.234 ml) was added. After being stirred at room temperature overnight, the resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1) to give ethyl 2-(benzyloxy)-5-[[4-[2-[benzyl(trifluoroacetyl)-amino]ethyl]phenyl]sulfonyl]benzoate (965 mg).

NMR ($CDCl_3$, δ): 1.33 (3H, t, J=7.1Hz), 2.75-2.95 (2H, m), 3.4-3.55 (2H, m), 4.36 (2H, q, J=7.1Hz), 4.45-4.70 (2H, m), 5.20 (2H, s), 7.07 (1H, d, J=8.9Hz), 7.1-7.5 (12H, m), 7.8-8.0 (3H, m), 8.32 (1H, d, J=2.4Hz)

(+)ESI-MS (m/z): 648 $(M+Na)^+$

Preparation 13

A mixture of ethyl 2-(benzyloxy)-5-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]benzoate (963 mg) and 10% palladium on activated carbon (50% wet, 100 mg) in ethanol (15 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 3 hours. After filtration, the filtrate was evaporated under reduced pressure followed by dryness in vacuo to give ethyl 5-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]phenyl]-sulfonyl]-2-hydroxybenzoate (848 mg).

NMR ($CDCl_3$, δ): 1.45 (3H, t, J=7.1Hz), 2.75-2.95 (2H, m), 3.4-3.55 (2H, m), 4.4-4.7 (3H, m), 7.05 (1H, d, J=8.9Hz), 7.1-7.45 (7H, m), 7.8-7.95 (3H, m), 8.47 (1H, d, J=2.4Hz)

(+)ESI-MS (m/z): 558 $(M+Na)^+$

Preparation 14

Under nitrogen, the mixture of ethyl 5-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (845 mg) and hydrogen chloride (7N in ethanol, 6 ml) in ethanol (3 ml) was refluxed for 2.5 days. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and chloroform/methanol (10:1). After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give ethyl 5-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (630 mg).

NMR (DMSO-d_6, δ): 1.33 (3H, t, J=7.1Hz), 2.65-2.9 (4H, m), 3.71 (2H, s), 4.35 (2H, q, J=7.1Hz), 7.09 (1H, d, J=8.8Hz), 7.15-7.3 (5H, m), 7.44 (2H, d, J=8.3Hz), 7.82 (2H, d, J=8.3Hz), 7.95 (1H, dd, J=2.5, 8.8Hz), 8.20 (1H, d, J=2.5Hz)

(+)ESI-MS (m/z): 440 $(M+H)^+$

Preparation 15

Under nitrogen at room temperature, to a solution of N-[2-[4-[[4-(benzyloxy)-3-hydroxyphenyl]sulfonyl]phenyl]-ethyl]-2,2,2-trifluoroacetamide (1.0 g) in N,N-dimethylformamide (10 ml) were added potassium carbonate (346 mg) and chloromethyl methyl ether (0.339 ml), and the mixture was stirred at the same temperature overnight. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give N-[2-[4-[[4-(benzyloxy)-3-(methoxymethoxy)phenyl]sulfonyl]phenyl]ethyl]-

2,2,2-trifluoroacetamide (1.1 g).

NMR ($CDCl_3$, δ): 2.85-3.0 (2H, m), 3.45-3.7 (5H, m), 5.15-5.3 (4H, m), 6.97 (1H, d, J=8.6Hz), 7.2-7.9 (11H, m)

(+)ESI-MS (m/z): 546 $(M+Na)^+$

Preparation 16

The following compounds were obtained according to a similar manner to that of Preparation 13.

(1) 2,2,2-Trifluoro-N-[2-[4-[[4-hydroxy-3-(methoxymethoxy)phenyl]sulfonyl]phenyl]ethyl]acetamide

NMR ($CDCl_3$, δ): 2.85-3.0 (3H, m), 3.45-3.65 (5H, m), 5.2 (2H, m), 7.02 (1H, d, J=8.4Hz), 7.31 (2H, d, J=8.2Hz), 7.45-7.65 (2H, m), 7.87 (2H, d, J=8.2Hz)

(-)ESI-MS (m/z): 432 $(M-H)^-$

(2) Ethyl (R)-4'-[[4-[2-(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.22 (3H, d, J=6.5Hz), 1.41 (3H, q, J=7.1Hz), 2.75-3.1 (2H, m), 4.15-4.5 (3H, m), 7.2-7.4 (2H, m), 7.54 (1H, t, J=7.7Hz), 7.65-8.15 (5H, m), 8.24 (1H, s)

(+)ESI-MS (m/z): 542 $(M+Na)^+$

(3) Ethyl 5-[[4-[3-[benzyl(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]-2-hydroxybenzoate

NMR ($CDCl_3$, δ): 1.45 (3H, t, J=7Hz), 1.68-2.02 (2H, m), 2.60 (2H, t, J=7Hz), 3.30 (2H, t, J=7Hz), 4.46 (2H, q, J=7Hz), 4.57, 4.61 (2H, a pair of s), 6.95-7.45 (9H, m), 7.83 (2H, m), 7.92 (1H, dd, J=9, 2Hz), 8.48 (1H, d, J=2Hz), 11.41 (1H, s, OH)

(+)ESI-MS (m/z): 572 $(M+Na)^+$

(4) 2,2,2-Trifluoro-N-[3-[4-[[4-hydroxy-3-

(methoxymethoxy)phenyl]sulfonyl]phenyl]propyl]acetamide
NMR ($CDCl_3$, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 3.52 (3H, s), 5.24 (2H, s), 6.33 (1H, br s), 6.43 (1H, s, OH), 7.03 (1H, d, J=9Hz), 7.29 (2H, d, J=8Hz), 7.55 (1H, dd, J=9, 2Hz), 7.66 (1H, d, J=2Hz), 7.83 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 470 $(M+Na)^+$

(5) Methyl 5-[[4-2-benzyl(trifluoroacetyl)amino]ethoxy]-phenyl]sulfonyl]-2-hydroxybenzoate
NMR ($CDCl_3$, δ): 3.60-3.85 (2H, m), 4.00 (3H, s), 4.04-4.25 (2H, m), 4.77, 4.81 (total 2H, a pair of s), 6.92 (2H, d, J=9Hz), 7.06 (1H, d, J=9Hz), 7.12-7.50 (5H, m), 7.85 (2H, d, J=8Hz), 7.93 (1H, dd, J=9, 2Hz), 8.46 (1H, d, J=2Hz), 11.25 (1H, br s, OH)
(+)ESI-MS (m/z): 560 $(M+Na)^+$

Preparation 17

The following compounds were obtained according to a similar manner to that of Preparation 10.

(1) 2-(Methoxymethoxy)-4-[[4-[2-[(trifluoroacetyl)amino]-ethyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate
NMR ($CDCl_3$, δ): 2.9-3.05 (2H, m), 3.5 (3H, m), 3.55-3.7 (2H, m), 5.30 (2H, s), 7.3-7.45 (3H, m), 7.60 (1H, dd, J=2.0, 8.5Hz), 7.8-7.95 (3H, m)
(+)ESI-MS (m/z): 588 $(M+Na)^+$

(2) 2-Methyl-4-[[4-[3-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate
NMR ($CDCl_3$, δ): 1.8-2.1 (2H, m), 2.43 (3H, s), 2.65-2.8 (2H, m), 3.35-3.5 (2H, m), 7.3-7.4 (3H, m), 7.8-7.95 (4H, m)

(+)ESI-MS (m/z): 556 $(M+Na)^+$

(3) tert-Butyl [4-[[(trifluoromethyl)sulfonyl]oxy]phenyl]-acetate

NMR ($CDCl_3$, δ): 1.44 (9H, s), 3.55 (2H, s), 7.2-7.4 (4H, m)

(+)ESI-MS (m/z): 363 $(M+Na)^+$

(4) (R)-2-Chloro-4-[[4-[2-(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate

NMR ($CDCl_3$, δ): 1.24 (3H, d, J=6.8Hz), 2.87 (1H, dd, J=7.3, 13.5Hz), 3.00 (1H, dd, J=6.2, 13.5Hz), 4.28 (1H, heptuplet, J=7.0Hz), 6.13 (1H, d, J=7.6Hz), 7.38 (2H, d, J=8.4Hz), 7.49 (1H, d, J=8.7Hz), 7.87-7.92 (3H, m), 8.09 (1H, d, J=2.2Hz)

(+)APCI-MS (m/z): 576 $(M+Na)^+$

(5) (R)-3-[[4-[2-[(2,2,2-Trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate

NMR ($CDCl_3$, δ): 1.22 (3H, d, J=6.8Hz), 2.8-3.05 (2H, m), 4.15-4.4 (1H, m), 7.36 (2H, d, J=8.3Hz), 7.45-7.5 (1H, m), 7.63 (1H, t, J=8.2Hz), 7.8-8.0 (4H, m)

(+)ESI-MS (m/z): 542 $(M+Na)^+$

(6) 2-Benzyloxy-5-[[4-[3-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate

NMR ($CDCl_3$, δ): 1.93 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 3.39 (2H, q, J=7Hz), 5.23 (2H, s), 6.29 (1H, br s), 7.08-7.50 (9H, m), 7.75-7.93 (3H, m)

(+)ESI-MS (m/z): 648 $(M+Na)^+$

(7) 2-Methoxymethoxy-4-[[4-[3-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]phenyl trifluoromethnesulfonate

NMR ($CDCl_3$, δ): 1.94 (2H, quintet, J=7Hz), 2.75 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 3.51 (3H, s), 5.30

(2H, s), 6.31 (1H, br s), 6.95 (1H, d, J=8Hz), 7.33 (2H, d, J=8Hz), 7.60 (1H, dd, J=8, 2Hz), 7.86 (1H, d, J=2Hz), 7.88 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 602 $(M+H)^+$

(8) 2-Chloro-4-[[4-[3-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate

NMR ($CDCl_3$, δ): 1.95 (2H, quintet, J=7Hz), 2.76 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 6.31 (1H, br s), 7.38 (2H, d, J=8Hz), 7.49 (1H, d, J=9Hz), 7.88 (2H, d, J=8Hz), 7.91 (1H, dd, J=9, 2Hz), 8.09 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 576 $(M+H)^+$

Preparation 18

The following compounds were obtained according to a similar manner to that of Preparation 11.

(1) Ethyl 2-(methoxymethoxy)-4-[[4-[2-[(trifluoroacetyl)amino]ethyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.36 (3H, t, J=7.1Hz), 2.96 (2H, t, J=7.1Hz), 3.50 (3H, s), 3.55-3.7 (2H, m), 4.36 (2H, q, J=7.1Hz), 5.28 (2H, s), 7.35 (2H, d, J=8.3Hz), 7.57 (1H, dd, J=1.5, 8.1Hz), 7.75 (1H, d, J=1.5Hz), 7.80 (1H, d, J=8.1Hz), 7.85-7.95 (2H, m)

(+)ESI-MS (m/z): 512 $(M+Na)^+$

(2) Ethyl 2-methyl-4-[[4-[3-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ):1.30 (3H, t, J=7.1Hz), 1.7-1.9 (2H, m), 2.55 (3H, m), 2.6-2.75 (2H, m), 3.1-3.25 (2H, m), 4.31 (2H, d, J=7.1Hz), 7.55-7.65 (2H, m), 7.8-8.0 (5H, m)

(+)ESI-MS (m/z): 480 $(M+Na)^+$

(3) Ethyl 2-benzyloxy-5-[[4-[3-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.34 (3H, t, J=7Hz), 1.91 (2H, quintet, J=7Hz), 2.71 (2H, t, J=7Hz), 3.37 (2H, q, J=7Hz), 4.36 (2H, q, J=7Hz), 5.21 (2H, s), 6.39 (1H, br s), 7.08 (1H, d, J=9Hz), 7.20-7.55 (7H, m), 7.84 (2H, d, J=8Hz), 7.98 (1H, dd, J=9, 2Hz), 8.33 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 572 $(M+Na)^+$

(4) Ethyl 2-methoxymethoxy-4-[[4-[3-[(trifluoroacetyl)-amino]propyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.36 (3H, t, J=7Hz), 1.92 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 3.50 (3H, s), 4.36 (2H, q, J=7Hz), 5.28 (2H, s), 6.37 (1H, br s), 7.33 (2H, d, J=8Hz), 7.55 (1H, dd, J=8, 2Hz), 7.75 (1H, d, J=2Hz), 7.79 (1H, d, J=2Hz), 7.86 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 526 $(M+Na)^+$

(5) Ethyl 2-chloro-4-[[4-[3-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.39 (3H, t, J=7Hz), 1.93 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 3.39 (2H, q, J=7Hz), 4.41 (2H, q, J=7Hz), 6.31 (1H, br s), 7.35 (2H, d, J=8Hz), 7.75-7.94 (4H, m), 8.00 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 500 $(M+Na)^+$

Preparation 19

The following compounds were obtained according to a similar manner to that of Preparation 12.

(1) Ethyl 4-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]-phenyl]sulfonyl]-2-(methoxymethoxy)benzoate

NMR ($CDCl_3$, δ): 1.35 (3H, t, J=7.2Hz), 2.75-2.95 (2H,

m), 3.4-3.55 (5H, m), 4.36 (2H, q, J=7.2Hz), 4.45-4.7 (2H, m), 5.27 (2H, s), 7.1-7.4 (7H, m), 7.45-7.55 (1H, m), 7.7-7.9 (4H, m)

(+)ESI-MS (m/z): 602 $(M+Na)^+$

(2) Ethyl 4'-[[4-[2-[benzyl(trifluoroacetyl)amino]ethyl]-phenyl]sulfonyl]-2'-(methoxymethoxy)1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.1Hz), 2.8-2.95 (2H, m), 3.37 (3H, s), 3.45-3.55 (2H, m), 4.36 (2H, q, J=7.1Hz), 4.5-4.7 (2H, m), 5.36 (2H, s), 7.15-7.5 (9H, m), 7.6-7.65 (2H, m), 7.75 (1H, m), 7.85-7.90 (2H, m), 8.05-8.1 (1H, m), 8.13 (1H, m)

(+)ESI-MS (m/z): 678 $(M+Na)^+$

(3) Ethyl 4-[[4-[3-[benzyl(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]-2-(methoxymethoxy)benzoate

NMR ($CDCl_3$, δ): 1.36 (3H, t, J=7Hz), 1.72-2.00 (2H, m), 2.59-2.66 (2H, a pair of t, J=7Hz), 3.31, 3.33 (2H, a pair of t, J=7Hz), 3.50 (3H, s), 4.36 (2H, q, J=7Hz), 4.57, 4.61 (2H, a pair of s), 5.28 (2H, s), 7.10-7.42 (7H, m), 7.55 (1H, dd, J=8, 2Hz), 7.70-7.95 (4H, m)

(4) Ethyl 2-benzyloxy-5-[[4-[3-[benzyl(trifluoroacetyl)-amino]propyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.34 (3H, t, J=7Hz), 1.65-2.00 (2H, m), 2.58 (2H, t, J=7Hz), 3.30 (2H, m), 4.36 (2H, q, J=7Hz), 4.56, 4.61 (2H, a pair of s), 5.21 (2H, s), 7.00-7.50 (13H, m), 7.81 (2H, m), 7.97 (1H, dd, J=9, 2Hz), 8.34 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 662 $(M+Na)^+$

Preparation 20

The following compounds were obtained according to a

similar manner to that of Preparation 14.

(1) Ethyl 4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR ($CDCl_3$, δ): 1.30 (3H, t, J=7.1Hz), 2.65-2.9 (4H, m), 3.68 (2H, s), 4.33 (2H, q, J=7.1Hz), 7.1-7.3 (5H, m), 7.35-7.05 (4H, m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 440 $(M+H)^+$

(2) Ethyl (R)-3-[4-[[4-(2-aminopropyl)phenyl]sulfonyl]-phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.12 (3H, d, J=6.2Hz), 1.38 (3H, t, J=7.2Hz), 2.5-2.7 (2H, m), 3.1-3.2 (1H, m), 4.37 (2H, q, J=7.2Hz), 6.95-7.1 (2H, m), 7.2-7.4 (3H, m), 7.47 (1H, t, J=8.0Hz), 7.7 (1H, m), 7.8-8.0 (5H, m)

(+)ESI-MS (m/z): 440 $(M+H)^+$

(3) Ethyl 4-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-methylbenzoate

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.1Hz), 1.6-1.85 (2H, m), 2.62 (3H, s), 2.65-2.8 (4H, m), 4.36 (2H, q, J=7.1Hz), 7.33 (2H, d, J=8.3Hz), 7.7-7.9 (4H, m), 7.96 (1H, d, J=8.1Hz)

(+)ESI-MS (m/z): 362 $(M+H)^+$

(4) (R)-Ethyl 3-[3-[[4-(2-aminopropyl)phenyl]sulfonyl]-phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.12 (3H, d, J=6.4Hz), 1.39 (3H, t, J=7.2Hz), 2.55-2.8 (2H, m), 3.1-3.3 (1H, m), 4.38 (2H, q, J=7.2Hz), 7.1-7.7 (9H, m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 440 $(M+H)^+$

(5) Ethyl (R)-4'-[[4-(2-aminopropyl)phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.12 (3H, d, J=6.2Hz), 1.41 (3H, t, J=7.2Hz), 2.5-2.8 (2H, m), 3.1-3.3 (1H, m), 4.41 (2H, q, J=7.2Hz), 7.35 (2H, d, J=8.3Hz), 7.54 (1H, t, J=7.8Hz), 7.7-8.15 (8H, m), 8.24 (1H, m)
(+)ESI-MS (m/z): 424 $(M+H)^+$

(6) Ethyl (R)-3'-[[4-(2-aminopropyl)phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.11 (3H, d, J=6.3Hz), 1.41 (3H, t, J=7.2Hz), 2.5-2.8 (2H, m), 3.1-3.25 (1H, m), 4.43 (2H, q, J=7.2Hz), 7.34 (2H, d, J=8.3Hz), 7.4-8.3 (10H, m)
(+)ESI-MS (m/z): 424 $(M+H)^+$

(7) Ethyl 4'-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate
NMR ($DMSO-d_6$, δ): 1.31 (3H, t, J=7.1Hz), 2.65-2.8 (4H, m), 3.69 (2H, s), 4.33 (2H, q, J=7.1Hz), 7.15-7.65 (11H, m), 7.75-8.0 (4H, m), 8.1-8.15 (1H, m)
(+)ESI-MS (m/z): 516 $(M+H)^+$

(8) Ethyl (R)-4-[[4-[(2-aminopropyl)oxy]phenyl]-sulfonyl]benzoate
NMR ($CDCl_3$, δ): 1.17 (3H, d, J=6.5Hz), 1.39 (3H, t, J=7.2Hz), 3.25-3.45 (1H, m), 3.65-3.8 (1H, m), 3.85-3.95 (1H, m), 4.39 (2H, q, J=7.2Hz), 6.95-7.0 (2H, m), 7.8-8.0 (4H, m), 8.1-8.2 (2H, m)
(+)ESI-MS (m/z): 364 $(M+H)^+$

(9) Ethyl 5-[[4-[3-(benzylamino)propyl]phenyl]sulfonyl]-2-hydroxybenzoate
NMR ($DMSO-d_6$, δ): 1.32 (3H, t, J=7Hz), 1.78 (2H, quintet, J=7Hz), 2.61 (2H, t, J=7Hz), 2.69 (2H, t, J=7Hz), 3.82 (2H, s), 4.33 (2H, q, J=7Hz), 7.07 (1H, d, J=9Hz), 7.20-7.42 (5H, m), 7.42 (2H, d,

J=8Hz), 7.82 (2H, d, J=8Hz), 7.91 (1H, dd, J=9, 2Hz), 8.19 (1H, d, J=2Hz)

(+)APCI-MS (m/z): 454 $(M+H)^+$

(10) Ethyl 4-[[4-[3-(benzylamino)propyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (DMSO-d_6, δ): 1.30 (3H, t, J=7Hz), 1.82 (2H, quintet, J=7Hz), 2.65 (2H, t, J=7Hz), 2.72 (2H, t, J=7Hz), 3.87 (2H, s), 4.33 (2H, q, J=7Hz), 7.10-7.55 (9H, m), 7.87 (2H, d, J=8Hz), 7.88 (1H, d, J=8Hz)

(11) Ethyl 5-[[4-[2-(benzylamino)ethoxy]phenyl]sulfonyl]-2-hydroxybenzoate

NMR ($CDCl_3$, δ): 1.45 (3H, t, J=7Hz), 3.03 (2H, t, J=5Hz), 3.87 (2H, s), 4.13 (2H, t, J=5Hz), 4.45 (2H, q, J=7Hz), 6.92 (2H, d, J=9Hz), 7.04 (1H, d, J=9Hz), 7.15-7.47 (5H, m), 7.84 (2H, d, J=9Hz), 7.90 (1H, dd, J=9, 2Hz), 8.46 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 456 $(M+H)^+$

(12) Ethyl 4-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-chlorobenzoate

NMR (DMSO-d_6, δ): 1.30 (3H, t, J=7Hz), 1.84 (2H, quintet, J=7Hz), 2.60-2.88 (4H, m), 4.35 (2H, q, J=7Hz), 7.51 (2H, d, J=8Hz), 7.85-8.10 (4H, m), 8.14 (1H, s)

(+)ESI-MS (m/z): 382 $(M+H)^+$

(13) Ethyl 5-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-methoxybenzoate

NMR (DMSO-d_6, δ): 1.29 (3H, t, J=7Hz), 1.67 (2H, quintet, J=7Hz), 2.35-2.80 (4H, m), 3.90 (3H, s), 4.28 (2H, q, J=7Hz), 7.36 (1H, d, J=9Hz), 7.44 (2H, d, J=8Hz), 7.86 (2H, d, J=8Hz), 8.09 (1H, dd, J=9,

2Hz), 8.12 (1H, d, J=2Hz)
(+)ESI-MS (m/z): 378 $(M+H)^+$

Preparation 21

To a solution of 2,2,2-trifluoro-N-[(1R)-1-methyl-2-phenylethyl]acetamide (3.75 g) in acetic acid (32 ml) - water (6.5 ml) - sulfuric acid (0.97 ml) were added iodine (1.65 g) and periodic acid dihydrate (740 mg) at room temperature, and the mixture was heated to 60-80°C for 5 hours. After being allowed to cool to room temperature, the mixture was partitioned between hexane/ethyl acetate and water. The organic layer was separated, washed successively with water, sodium sulfite solution, water, and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was recrystallized from diisopropyl ether (44 ml) to give 2,2,2-trifluoro-N-[(1R)-2-(4-iodophenyl)-1-methylethyl]acetamide (2.15 g) as a colorless needle.

NMR ($CDCl_3$, δ): 1.21 (3H, d, J=7Hz), 2.74 (1H, dd, J=14, 7Hz), 2.85 (1H, dd, J=14, 6Hz), 4.26 (1H, m), 6.04 (1H, br s), 6.92 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 380 $(M+Na)^+$

Preparation 22

Under nitrogen at room temperature, to a mixture of bis(dibenzylideneacetone)palladium(0) (403 mg) and bis(2-diphenylphosphinophenyl)ether (407 mg) was added toluene (90 ml). After being stirred at the same temperature for 15 minutes, (R)-2,2,2-trifluoro-N-[2-(4-iodophenyl)-1-methylethyl]acetamide (5 g), potassium tert-butoxide (1.89 g) and 4-methoxybenzenethiol (1.89 ml) were added, and the mixture was stirred at 80°C for 3 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed

successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1 to 5:1) to give (R)-2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]-1-methylethyl]acetamide (4.39 g).

NMR (DMSO-d_6, δ): 1.14 (3H, d, J=6.7Hz), 2.73 (2H, d, J=7.1Hz), 3.77 (3H, s), 3.9-4.1 (1H, m), 6.9-7.2 (6H, m), 7.3-7.4 (2H, m)

(+)ESI-MS (m/z): 392 $(M+H)^+$

Preparation 23

Under nitrogen at 5°C, to a solution of (R)-2,2,2-trifluoro-N-[2-[4-[(4-methoxyphenyl)thio]phenyl]-1-methylethyl]acetamide (4.38 g) in dichloromethane (88 ml) was added boron tribromide (1M in dichloromethane, 35.6 ml) dropwise, and the mixture was stirred at room temperature overnight. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give (R)-2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]-1-methylethyl]acetamide (3.97 g).

NMR ($CDCl_3$, δ): 1.20 (3H, d, J=6.6Hz), 2.65-2.9 (2H, m), 4.1-4.35 (1H, m), 6.75-6.9 (2H, m), 6.95-7.15 (4H, m), 7.3-7.4 (2H, m)

(+)ESI-MS (m/z): 378 $(M+Na)^+$

Preparation 24

A mixture of (R)-2,2,2-trifluoro-N-[2-[4-[(4-hydroxyphenyl)thio]phenyl]-1-methylethyl]acetamide (500 mg), 3-ethoxycarbonylphenylboronic acid (546 mg), copper(II) acetate (256 mg), powdered molecular sieves 4 Å (500 mg) and

pyridine (0.569 ml) in dichloromethane (15 ml) was stirred at room temperature for 4 days. After the resulting mixture was filtered with celite, the filtrate was poured into 0.1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1) to give ethyl (R)-3-[4-[[4-[2-[(trifluoroacetyl)amino]propyl]-phenyl]thio]phenoxy]benzoate (463 mg).

NMR ($CDCl_3$, δ): 1.22 (3H, d, J=6.6Hz), 1.39 (3H, t, J=6.9Hz), 2.7-2.95 (2H, m), 4.15-4.45 (3H, m), 6.9-7.85 (12H, m)

(+)ESI-MS (m/z): 526 $(M+Na)^+$

Preparation 25

The following compounds were obtained according to a similar manner to that of Preparation 6.

(1) Ethyl (R)-3-[4-[[4-[2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.22 (3H, d, J=6.6Hz), 1.37 (3H, t, J=7.1Hz), 2.75-3.05 (2H, m), 4.15-4.45 (3H, m), 6.95-7.1 (2H, m), 7.2-7.4 (3H, m), 7.47 (1H, t, J=8.0Hz), 7.7 (1H, m), 7.85-7.95 (5H, m)

(+)ESI-MS (m/z): 558 $(M+Na)^+$

(2) tert-Butyl benzyl[2-[4-[[4-(2-formylphenoxy)phenyl]-sulfonyl]phenyl]ethyl]carbamate

NMR ($CDCl_3$, δ): 1.41 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 4.25-4.5 (2H, m), 6.95-7.4 (10H, m), 7.5-7.65 (1H, m), 7.75-8.0 (6H, m), 10.31 (1H, s)

(+)ESI-MS (m/z): 594 $(M+Na)^+$

(3) tert-Butyl benzyl[2-[4-[[3-(2-formylphenoxy)phenyl]-sulfonyl]phenyl]ethyl]carbamate

NMR ($CDCl_3$, δ): 1.40 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 4.25-4.5 (2H, m), 6.85-8.0 (17H, m), 10.40 (1H, s)

(+)ESI-MS (m/z): 594 $(M+H)^+$

(4) tert-Butyl [4-[[4-[2-[benzyl(tert-butoxycarbonyl)-amino]ethyl]phenyl]sulfonyl]phenyl]acetate

NMR ($CDCl_3$, δ): 1.39 (9H, br s), 1.42 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 3.56 (2H, s), 4.25-4.45 (2H, m), 7.1-7.35 (9H, m), 7.8-7.95 (4H, m)

(+)ESI-MS (m/z): 588 $(M+Na)^+$

(5) Ethyl (R)-3-[3-[[4-[2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.21 (3H, d, J=6.6Hz), 1.39 (3H, t, J=7.2Hz), 2.8-3.05 (2H, m), 4.2-4.45 (3H, m), 7.1-7.7 (9H, m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 558 $(M+Na)^+$

(6) tert-Butyl benzyl[2-[4-[(3-hydroxyphenyl)sulfonyl]-phenyl]ethyl]carbamate

NMR ($CDCl_3$, δ): 1.38 (9H, br s), 2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 4.37 (2H, br s), 6.95-7.05 (1H, m), 7.15-7.5 (10H, m), 7.75-7.85 (2H, m)

(+)ESI-MS (m/z): 490 $(M+Na)^+$

(7) Ethyl 4-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.3-1.45 (12H, m), 2.7-2.9 (2H, m), 3.3-3.5 (2H, m), 4.3-4.5 (4H, m), 6.95-7.05 (2H, m), 7.1-7.75 (13H, m), 7.82 (2H, d, J=8.2Hz), 8.0-8.1 (2H, m)

(+)ESI-MS (m/z): 638 $(M+Na)^+$

(8) Ethyl 3-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoate
NMR ($CDCl_3$, δ): 1.3-1.5 (12H, m), 2.7-2.95 (2H, m), 3.3-3.5 (2H, m), 4.25-4.5 (4H, m), 7.1-7.7 (14H, m), 7.75-7.9 (3H, m)
(+)ESI-MS (m/z): 638 $(M+Na)^+$

(9) tert-Butyl benzyl[2-[4-[(4-hydroxyphenyl)sulfonyl]-phenyl]ethyl]carbamate
(+)ESI-MS (m/z): 490 $(M+Na)^+$

(10) 2,2,2-Trifluoro-N-[3-[4-[(3-methoxyphenyl)sulfonyl]-phenyl]propyl]acetamide
NMR ($CDCl_3$, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.39 (2H, q, J=7Hz), 3.84 (3H, s), 6.31 (1H, br s), 7.00-7.16 (1H, m), 7.20-7.58 (5H, m), 7.86 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 424 $(M+Na)^+$

(11) tert-Butyl benzyl[2-[4-[(4-hydroxyphenyl)sulfonyl]-phenoxy]ethyl]carbamate
NMR ($CDCl_3$, δ): 1.45 (9H, s), 3.58 (2H, br s), 4.08 (2H, br s), 4.53 (2H, s), 6.86 (2H, d, J=8Hz), 6.89 (2H, d, J=8Hz), 7.10-7.42 (5H, m), 7.64-7.90 (4H, m)
(+)ESI-MS (m/z): 506 $(M+Na)^+$

(12) Methyl 2-benzyloxy-5-[[4-[2-[benzyl(trifluoroacetyl)-amino]ethoxy]phenyl]sulfonyl]benzoate
NMR ($CDCl_3$, δ): 3.60-3.85 (2H, m), 3.91 (3H, s), 4.03-4.23 (2H, m), 4.77, 4.81 (total 2H, a pair of s), 5.23 (2H, s), 6.91 (2H, d, J=9Hz), 7.07 (1H, d, J=9Hz), 7.14-7.52 (10H, m), 7.85 (2H, d, J=8Hz), 7.96 (1H, dd, J=9, 2Hz), 8.35 (1H, d, J=2Hz)
(+)ESI-MS (m/z): 650 $(M+Na)^+$

Preparation 26

Under nitrogen at room temperature, to a solution of 4-fluorobenzaldehyde (3.0 g) in N,N-dimethylformamide (60 ml) was added 4-methoxybenzenethiol (3.3 ml) and potassium carbonate (3.7 g), and the mixture was stirred at 120°C for 6 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatgraphy on silica gel (hexane:ethyl acetate = 10:1) to give 4-[(4-methoxyphenyl)thio]benzaldehyde (4.9 g).

NMR ($CDCl_3$, δ): 3.86 (3H, s), 6.95-7.0 (2H, m), 7.1-7.2 (2H, m), 7.45-7.5 (2H, m), 7.65-7.7 (2H, m), 9.89 (1H, s)

(+)APCI-MS (m/z): 245 $(M+H)^+$

Preparation 27

Under nitrogen at room temperature, to a solution of 4-[(4-methoxyphenyl)thio]benzaldehyde (5.1 g) in methanol (51 ml) were added nitromethane (1.7 ml), acetic acid (0.60 ml) and butylamine (1.0 ml), and the mixture was stirred at the same temperature overnight to give precipitates. Water (51 ml) was poured into the resulting mixture and the mixture was the mixture was stirred for 30 minutes. The deposits were collected by filtration and the filter cake was washed with water followed by air-drying to give 1-methoxy-4-[[4-(2-nitroethenyl)phenyl]thio]benzene (5.4 g).

NMR ($CDCl_3$, δ): 3.86 (3H, s), 6.9-7.15 (4H, m), 7.3-7.6 (5H, m), 7.85-7.95 (1H, m)

(+)ESI-MS (m/z): 310 $(M+Na)^+$

Preparation 28

Under nitrogen at 5°C, to a suspension of lithium

aluminum hydride (3.2 g) in tetrahydrofuran (80 ml) was added dropwise 1-methoxy-4-[[4-(2-nitroethenyl)phenyl]thio]-benzene (4.8 g) in tetrahydrofuran (50 ml), and the mixture was refluxed for 6.5 hours. The resulting mixture was cooled to 5°C, and to this one was added sodium fluoride (14 g) followed by water (4.5 ml) dropwise carefully. The mixture was vigorously stirred at room temperature for 30 minutes. The precipitates were removed by filtration, and the filter cake was washed with a mixture of ethyl acetate and ethanol (95:5). The filtrate was evaporated under reduced pressure. The residue was dissolved into ethyl acetate (40 ml) and cooled to 5°C. To this one was added 4N hydrogen chloride in 1,4-dioxane (8.4 ml) and the mixture was stirred at room temperature for 30 minutes to deposit the corresponding salt followed by collection by filtration. The filter cake was washed with ethyl acetate and dissolved into a mixture of ethyl acetate and 1N sodium hydroxide. After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried to give 2-[4-[(4-methoxyphenyl)thio]phenyl]ethylamine (2.0 g).

NMR ($CDCl_3$, δ): 2.69 (2H, t, J=6.8Hz), 2.93 (2H, t, J=6.8Hz), 3.81 (3H, s), 6.85-6.95 (2H, m), 7.05-7.2 (4H, m), 7.35-7.45 (2H, m)

(+)APCI-MS (m/z): 260 $(M+H)^+$

Preparation 29

Under nitrogen at room temperature, to a solution of 2-[4-[(4-methoxyphenyl)thio]phenyl]ethylamine (2.0 g) in dichloromethane (20 ml) was added benzaldehyde (0.78 ml), and the mixture was stirred at the same temperature for 20 minutes. To this one was added toluene and evaporated under reduced pressure. Under nitrogen at 5°C, to a solution of the residue in tetrahydrofuran (20 ml) was added sodium borohydride (0.32 g) followed by methanol (10 ml) dropwise

and the mixture was stirred at room temperature for 40 minutes. The resulting mixture was poured into a mixture of ethyl acetate and water, and stirred for 10 minutes. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol = 100:1 to 20:1) to give N-benzyl-N-[2-[4-[(4-methoxyphenyl)thio]-phenyl]ethyl]amine (2.0 g).

NMR ($CDCl_3$, δ): 2.7-2.9 (4H, m), 3.81 (2H, s), 3.83 (3H, s), 6.85-6.95 (2H, m), 7.05-7.45 (11H, m)

(+)APCI-MS (m/z): 350 $(M+H)^+$

Preparation 30

The following compounds were obtained according to a similar manner to that of Preparation 23.

(1) 4-[[4-[2-(Benzylamino)ethyl]phenyl]thio]phenol

NMR (DMSO-d_6, δ): 2.65-2.75 (4H, m), 3.71 (2H, s), 6.75-6.85 (2H, m), 6.95-7.35 (11H, m)

(+)APCI-MS (m/z): 336 $(M+H)^+$

(2) 3-[[4-[2-(Benzylamino)ethyl]phenyl]thio]phenol

NMR (DMSO-d_6, δ): 2.7-2.85 (4H, m), 3.74 (2H, s), 7.55-7.75 (3H, m), 7.05-7.4 (10H, m)

(+)APCI-MS (m/z): 336 $(M+H)^+$

(3) 2,2,2-Trifluoro-N-[3-[4-[(4-hydroxy-3-methylphenyl)sulfonyl]phenyl]propyl]acetamide

NMR ($CDCl_3$, δ): 1.8-2.0 (2H, m), 2.24 (3H, s), 2.6-2.75 (2H, m), 3.3-3.45 (2H, m), 6.83 (1H, d, J=8.3Hz), 7.25-7.3 (2H, m), 7.6-7.7 (2H, m), 7.75-7.9 (2H, m)

(+)ESI-MS (m/z): 424 $(M+Na)^+$

(4) (R)-2,2,2-Trifluoro-N-[2-[4-[(3-hydroxyphenyl)thio]-phenyl]-1-methylethyl]acetamide
NMR ($CDCl_3$, δ): 1.30 (3H, d, J=6.7Hz), 2.65-2.95 (2H, m), 4.15-4.4 (1H, m), 6.3 (1H, m), 6.6-6.65 (1H, m), 6.8-6.85 (1H, m), 7.05-7.2 (3H, m), 7.35-7.45 (2H, m)
(+)ESI-MS (m/z): 378 $(M+Na)^+$

(5) (R)-N-[2-[4-[(3-Chloro-4-hydroxyphenyl)sulfonyl]-phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide
(+)APCI-MS (m/z): 444 $(M+Na)^+$

(6) 3-[[4-[3-(Benzylamino)propyl]phenyl]sulfonyl]phenol
NMR (DMSO-d_6, δ): 1.75 (2H, quintet, J=7Hz), 2.55 (2H, t, J=7Hz), 2.66 (2H, t, J=7Hz), 3.76 (2H, s), 6.95-7.11 (1H, m), 7.11-7.55 (10H, m), 7.81 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 382 $(M+H)^+$

(7) 2-[[4-[(2R)-2-(Benzylamino)propyl]phenyl]sulfonyl]-phenol
NMR (DMSO-d_6, δ): 0.95 (3H, d, J=7Hz), 2.40-3.00 (3H, m), 3.76 (1H, d, J=14Hz), 3.80 (1H, d, J=14Hz), 6.88 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz), 7.05-7.35 (5H, m), 7.37 (2H, d, J=8Hz), 7.48 (1H, t, J=8Hz), 7.80 (2H, d, J=8Hz), 7.89 (1H, d, J=8Hz)
(+)ESI-MS (m/z): 382 $(M+H)^+$

(8) N-[3-[4-[(3-Chloro-4-hydroxyphenyl)sulfonyl]phenyl]-propyl]-2,2,2-trifluroacetamide
NMR ($CDCl_3$, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 6.15 (1H, s, OH), 6.33 (1H, br s), 7.10 (1H, d, J=9Hz), 7.32 (2H, d, J=8Hz), 7.75 (1H, dd, J=9, 2Hz), 7.83 (2H, d, J=8Hz), 7.93 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 444 $(M+Na)^+$

Preparation 31

Under nitrogen at room temperature, to a solution of 4-[[4-[2-(benzylamino)ethyl]phenyl]thio]phenol (794 mg) in tetrahydrofuran (8 ml) was added di-tert-butyl dicarbonate (775 mg) in tetrahydrofuran (2 ml), and the mixture was stirred at the same temperature for 9.5 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1 to 2:1) to give tert-butyl benzyl[2-[4-[(4-hydroxyphenyl)thio]phenyl]ethyl]carbamate (849 mg).

NMR ($CDCl_3$, δ): 1.45 (9H, s), 2.6-2.85 (2H, m), 3.25-3.45 (2H, m), 4.3-4.45 (2H, m), 6.75-6.85 (2H, m), 6.9-7.4 (11H, m)

(+)ESI-MS (m/z): 458 $(M+Na)^+$

Preparation 32

Under nitrogen at room temperature, to a solution of tert-butyl benzyl[2-[4-[(4-hydroxyphenyl)thio]phenyl]-ethyl]carbamate (1.8 g) in N,N-dimethylformamide (20 ml) were added potassium carbonate (628 mg) and 2-fluorobenzaldehyde (0.497 ml), and the mixture was stirred at 130°C for 1.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1 to 5:1) to give tert-butyl benzyl[2-[4-[[4-(2-formylphenoxy)phenyl]thio]phenyl]ethyl]-carbamate (1.76 g).

NMR ($CDCl_3$, δ): 1.46 (9H, s), 2.6-2.9 (2H, m), 3.25-3.5 (2H, m), 4.25-4.45 (2H, m), 6.9-7.4 (15H, m),

7.45-7.6 (1H, m), 7.9-8.0 (1H, m), 10.47 (1H, s)
(+)ESI-MS (m/z): 562 $(M+Na)^+$

Preparation 33

To a solution of tert-butyl benzyl[2-[4-[[4-(2-formylphenoxy)phenyl]sulfonyl]phenyl]ethyl]carbamate (1.17 g) in acetonitrile (18 ml) were added sodium dihydrogenphosphate (51.6 mg) and 30% hydrogen peroxide (0.232 ml) at room temperature. After the mixture was cooled to 5°C, sodium chlorite (333 mg) in water (18 ml) was added dropwise and the mixture was stirred at room temperature for 2.5 days. To the resulting mixture was added sodium sulfite, and the mixture was stirred for 10 minutes, followed by being adjusted pH to around 2.5 with 1N hydrochloric acid to give deposits. The precipitates were collected and washed with water followed by dryness in vacuo to give 2-[4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoic acid (1.0 g).

NMR (DMSO-d_6, δ): 1.0-1.4 (9H, m), 2.7-2.9 (2H, m), 3.1-3.45 (2H, m), 4.25-4.5 (2H, m), 6.8-7.5 (10H, m), 7.55-8.0 (7H, m)
(-)ESI-MS (m/z): 586 $(M-H)^-$

Preparation 34

Under nitrogen at room temperature, to a solution of 2-[4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]-phenyl]sulfonyl]phenoxy]benzoic acid (1.0 g) in N,N-dimethylformamide (10 ml) were added potassium carbonate (282 mg) and iodoethane (0.15 ml), and the mixture was stirred at the same temperature for 2.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column

chromatography on silica gel (hexane/ethyl acetate = 3:1 to 12:5) to give ethyl 2-[4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]sulfonyl]-phenoxy]benzoate (783 mg).

NMR ($CDCl_3$, δ): 1.06 (3H, t, J=7.1Hz), 1.41 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 4.16 (2H, q, J=7.1Hz), 4.25-4.5 (2H, m), 6.85-7.4 (11H, m), 7.5-7.6 (1H, m), 7.75-8.0 (5H, m)

(+)ESI-MS (m/z): 638 $(M+Na)^+$

Preparation 35

The following compounds were obtained according to a similar manner to that of Preparation 7.

(1) Ethyl 2-[4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.06 (3H, t, J=7.1Hz), 2.8-2.95 (4H, m), 3.79 (2H, s), 4.16 (2H, q, J=7.1Hz), 6.85-7.1 (3H, m), 7.2-7.4 (8H, m), 7.5-7.6 (1H, m), 7.75-9.9 (5H, m)

(+)ESI-MS (m/z): 516 $(M+H)^+$

(2) Ethyl 2-[3-[[4-[2-(benzylamino)ethyl]phenyl]-sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.04 (3H, t, J=7.2Hz), 2.8-2.95 (4H, m), 3.79 (2H, s), 4.05-4.2 (2H, m), 6.95-7.1 (2H, m), 7.2-7.65 (12H, m), 7.75-7.85 (2H, m), 7.9-8.0 (1H, m)

(+)ESI-MS (m/z): 516 $(M+H)^+$

(3) 3-[[4-[2-(Benzylamino)ethyl]phenyl]sulfonyl]phenol

NMR ($CDCl_3$, δ): 2.7-3.0 (4H, m), 3.81 (2H, s), 6.9-7.0 (1H, m), 7.1-7.5 (10H, m), 7.75-7.85 (2H, m)

(-)APCI-MS (m/z): 366 $(M-H)^-$

(4) Ethyl 4-[3-[[4-[2-(benzylamino)ethyl]phenyl]-sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.40 (3H, t, J=7.1Hz), 2.8-2.95 (4H, m), 3.79 (2H, s), 4.38 (2H, q, J=7.1Hz), 6.95-7.05 (2H, m), 7.15-7.4 (8H, m), 7.48 (1H, t, J=8.0Hz), 7.55-7.75 (2H, m), 7.84 (2H, d, J=8.4Hz), 8.0-8.1 (2H, m)

(+)ESI-MS (m/z): 516 $(M+H)^+$

(5) Ethyl 3-[3-[[4-[2-(benzylamino)ethyl]phenyl]-sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.1Hz), 2.8-2.95 (4H, m), 3.79 (2H, s), 4.37 (2H, q, J=7.1Hz), 7.1-7.7 (14H, m), 7.8-7.9 (3H, m)

(+)ESI-MS (m/z): 516 $(M+H)^+$

(6) (R)-1-Phenoxy-2-propanamine

NMR (DMSO-d_6, δ): 1.05 (3H, d, J=6.4Hz), 3.05-3.2 (1H, m), 3.65-3.8 (2H, m), 6.85-7.0 (3H, m), 7.25-7.4 (2H, m)

(+)ESI-MS (m/z): 152 $(M+H)^+$

(7) 4-[[4-[2-(Benzylamino)ethyl]phenyl]sulfonyl]phenol

(+)ESI-MS (m/z): 368 $(M+H)^+$

(8) 4-[[4-[2-(Benzylamino)ethoxy]phenyl]sulfonyl]phenol

NMR (DMSO-d_6, δ): 2.85 (2H, t, J=6Hz), 3.57 (2H, s), 4.10 (2H, t, J=6Hz), 6.90 (2H, d, J=8Hz), 7.09 (2H, d, J=8Hz), 7.15-7.40 (5H, m), 7.72 (2H, d, J=8Hz), 7.79 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 384 $(M+H)^+$

Preparation 36

The following compound was obtained according to a similar manner to that of Preparation 26.

4-[(3-Methoxyphenyl)thio]benzaldehyde

NMR ($CDCl_3$, δ): 3.81 (3H, s), 6.9-7.0 (1H, m), 7.05-7.15 (2H, m), 7.25-7.4 (3H, m), 7.7-7.8 (2H, m), 9.92 (1H, s)

(+)APCI-MS (m/z): 245 $(M+H)^+$

Preparation 37

The following compound was obtained according to a similar manner to that of Preparation 27.

1-Methoxy-3-[[4-(2-nitroethenyl)phenyl]thio]benzene

NMR ($CDCl_3$, δ): 3.80 (3H, s), 6.85-7.15 (3H, m), 7.2-7.55 (6H, m), 7.9-8.0 (1H, m)

(+)ESI-MS (m/z): 310 $(M+Na)^+$

Preparation 38

The following compound was obtained according to a similar manner to that of Preparation 28.

2-[4-[(3-Methoxyphenyl)thio]phenyl]ethylamine

NMR ($CDCl_3$, δ): 2.74 (2H, t, J=6.9Hz), 2.97 (2H, t, J=6.9Hz), 3.75 (3H, s), 6.7-6.9 (3H, m), 7.1-7.4 (5H, m)

(+)ESI-MS (m/z): 260 $(M+H)^+$

Preparation 39

The following compounds were obtained according to a similar manner to that of Preparation 29.

(1) N-Benzyl-N-[2-[4-[(3-methoxyphenyl)thio]phenyl]ethyl]-amine

NMR ($CDCl_3$, δ): 2.75-3.0 (4H, m), 3.78 (3H, s), 3.80 (2H, s), 6.7-6.95 (3H, m), 7.1-7.4 (10H, m)

(+)APCI-MS (m/z): 350 $(M+H)^+$

(2) N-Benzyl-N-[3-[4-[(3-methoxyphenyl)sulfonyl]phenyl]-propyl]amine

NMR ($CDCl_3$, δ): 1.81 (2H, quintet, J=7Hz), 2.52-2.80 (4H, m), 3.77 (2H, s), 3.84 (3H, s), 7.00-7.12 (1H, m), 7.15-7.55 (10H, m), 7.83 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 396 $(M+H)^+$

(3) N-Benzyl-N-[(1R)-2-[4-[(2-methoxyphenyl)sulfonyl]-phenyl]-1-methylethyl]amine

NMR ($CDCl_3$, δ): 1.07 (3H, d, J=6Hz), 2.68 (1H, dd, J=13, 6Hz), 2.82 (1H, dd, J=13, 7Hz), 2.94 (1H, m), 3.72 (1H, d, J=13Hz), 3.73 (3H, s), 3.83 (1H, d, J=13Hz), 6.89 (1H, d, J=8Hz), 7.10-7.43 (7H, m), 7.14 (1H, t, J=8Hz), 7.54 (1H, t, J=8Hz), 7.88 (2H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 396 $(M+H)^+$

Preparation 40

The following compound was obtained according to a similar manner to that of Preparation 31.

tert-Butyl benzyl[2-[4-[(3-hydroxyphenyl)thio]phenyl]ethyl]carbamate

NMR ($CDCl_3$, δ): 1.45 (9H, br s), 2.7-2.85 (2H, m), 3.3-3.5 (2H, m), 4.37 (2H, s), 6.55-6.7 (2H, m), 6.75-6.85 (1H, m), 7.05-7.4 (10H, m)

(+)ESI-MS (m/z): 458 $(M+Na)^+$

Preparation 41

The following compound was obtained according to a similar manner to that of Preparation 32.

tert-Butyl benzyl[2-[4-[[3-(2-formylphenoxy)phenyl]thio]phenyl]ethyl]carbamate

NMR ($CDCl_3$, δ): 1.47 (9H, s), 2.65-2.9 (2H, m), 3.25-3.5 (2H, m), 4.25-4.5 (2H, m), 6.8-7.6 (16H, m), 7.85-7.95 (1H, m), 10.45 (1H, s)

(+)ESI-MS (m/z): 562 $(M+H)^+$

Preparation 42

The following compound was obtained according to a similar manner to that of Preparation 33.

2-[3-[[4-[2-[Benzyl(tert-butoxycarbonyl)amino]ethyl]-phenyl]sulfonyl]phenoxy]benzoic acid

NMR ($CDCl_3$, δ): 1.0-1.4 (9H, m), 2.7-2.95 (2H, m), 3.2-3.5 (2H, m), 4.25-4.45 (2H, m), 6.8-8.0 (17H, m)

(-)ESI-MS (m/z): 586 $(M-H)^-$

Preparation 43

The following compound was obtained according to a similar manner to that of Preparation 34.

Ethyl 2-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.06 (3H, t, J=7.1Hz), 1.42 (9H, s), 2.7-2.9 (2H, m), 3.25-3.5 (2H, m), 4.15 (2H, q, J=7.1Hz), 4.25-4.5 (2H, m), 7.0-7.1 (2H, m), 7.1-7.6 (12H, m), 7.75-7.85 (2H, m), 7.9-8.0 (1H, m)

(+)ESI-MS (m/z): 638 $(M+Na)^+$

Preparation 44

Under nitrogen at room temperature, to a solution of (R)-2,2,2-trifluoro-N-(1-methyl-2-phenylethyl)acetamide (1.5 g) and methyl 5-(chlorosulfonyl)-2-hydroxybenzoate (2.18 g) in 1,2-dichloroethane (15 ml) was added aluminum chloride (3.03 g), and the mixture was stirred at 60-65°C for 4.5 hours. After the resulting mixture was cooled to room temperature, chloroform and water were added, followed by

being stirred for 30 minutes. After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/ethyl acetate = 20:1) to give methyl (R)-2-hydroxy-5-[[4-[2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (2.12 g).

NMR ($CDCl_3$, δ): 1.21 (3H, d, J=6.7Hz), 2.75-3.05 (2H, m), 3.98 (3H, s), 4.15-4.4 (1H, m), 7.07 (1H, d, J=8.8Hz), 7.32 (2H, d, J=8.3Hz), 7.87 (2H, d, J=8.3Hz), 7.95 (1H, dd, J=2.4, 8.9Hz), 8.48 (1H, d, J=2.4Hz)

(+)ESI-MS (m/z): 468 $(M+Na)^+$

Preparation 45

Under nitrogen at room temperature, a mixture of methyl (R)-2-hydroxy-5-[[4-[2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]benzoate (2.1 g) and 7N hydrogen chloride in ethanol (40 ml) was refluxed for 12 hours. The resulting mixture was evaporated under reduced pressure followed by dryness in vacuo to give ethyl (R)-5-[[4-(2-aminopropyl)-phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (1.97 g).

NMR (DMSO-d_6, δ): 1.11 (3H, d, J=6.5Hz), 1.34 (3H, t, J=7.1Hz), 2.8-3.55 (3H, m), 4.37 (2H, q, J=7.1Hz), 7.22 (1H, d, J=8.7Hz), 7.51 (2H, d, J=8.3Hz), 7.85-8.3 (3H, m)

(+)ESI-MS (m/z): 364 $(M-HCl+H)^+$

Preparation 46

Ethyl (R)-5-[[4-(2-aminopropyl)phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (1.96 g) was dissolved into a mixture of chloroform/methanol (4:1) and water, and sodium bicarbonate (412 mg) was added. After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Under nitrogen, a

mixture of the residue and (R)-2-(3-chlorophenyl)oxirane (758 mg) in ethanol (34 ml) was stirred at 70°C for 19.5 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1) to give ethyl 5-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-propyl]phenyl]sulfonyl]-2-hydroxybenzoate (810 mg).

NMR ($CDCl_3$, δ): 1.05 (3H, d, J=6.1Hz), 1.45 (3H, t, J=7.2Hz), 2.55-3.0 (5H, m), 4.35-4.6 (3H, m), 7.06 (1H, d, J=8.9Hz), 7.1-7.35 (6H, m), 7.8-8.0 (3H, m), 8.50 (1H, d, J=2.3Hz)

(+)ESI-MS (m/z): 518, 520 $(M+H)^+$

Preparation 47

Under nitrogen at room temperature, to a solution of 3-phenyl-1-propylamine (100 g) in methanol (500 ml) was added ethyl trifluoroacetate (106 ml) dropwise, and the mixture was stirred at the same temperature for 4 hours. The resulting mixture was evaporated under reduced pressure and dried in vacuo to give 2,2,2-trifluoro-N-(3-phenylpropyl)-acetamide (171 g).

NMR ($CDCl_3$, δ): 1.85-2.0 (2H, m), 2.69 (2H, t, J=7.4Hz), 3.3-3.5 (2H, m), 7.15-7.4 (5H, m)

(+)ESI-MS (m/z): 254 $(M+Na)^+$

Preparation 48

Under nitrogen at 5°C, to a solution of 2,2,2-trifluoro-N-(3-phenylpropyl)acetamide (100 g) in chloroform (800 ml) was added chlorosulfonic acid (144 ml) dropwise, and the mixture was stirred at the same temperature for 1 hour and at room temperature for 36 hours. The resulting mixture was carefully poured into a stirred mixture of water and chloroform under ice-water cooling. After separation, the organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure.

The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1 to 2:1) to give 4-[3-[(trifluoroacetyl)amino]propyl]benzenesulfonyl chloride (109 g).

NMR ($CDCl_3$, δ): 1.9-2.1 (2H, m), 2.81 (2H, t, J=7.4Hz), 3.35-3.55 (2H, m), 7.4-7.5 (2H, m), 7.95-8.05 (2H, m)

Preparation 49

The following compounds were obtained according to a similar manner to that of Preparation 44.

(1) 2,2,2-Trifluoro-N-[3-[4-[(4-methoxy-3-methylphenyl)sulfonyl]phenyl]propyl]acetamide

NMR ($CDCl_3$, δ): 1.8-2.0 (2H, m), 2.21 (3H, s), 2.6-2.75 (2H, m), 3.3-3.45 (2H, m), 3.86 (3H, s), 6.87 (1H, d, J=8.6Hz), 7.25-7.3 (2H, m), 7.65 (1H, m), 7.75-7.9 (3H, m)

(+)ESI-MS (m/z): 438 $(M+Na)^+$

(2) (R)-N-[2-[4-[(3-Chloro-4-methoxyphenyl)sulfonyl]-phenyl]-1-methylethyl]-2,2,2-trifluoroacetamide

(+)APCI-MS (m/z): 458 $(M+Na)^+$

(3) (R)-4-[[4-[[2-[(Trifluoroacetyl)amino]propyl]oxy]-phenyl]sulfonyl]benzoic acid

NMR (DMSO-d_6, δ): 1.1-1.3 (3H, m), 3.9-4.4 (3H, m), 7.1-7.3 (2H, m), 7.85-8.2 (6H, m)

(-)ESI-MS (m/z): 430 $(M-H)^-$

(4) N-[3-[4-[(3,4-Dihydroxyphenyl)sulfonyl]phenyl]propyl]-2,2,2-trifluoroacetamide

NMR (DMSO-d_6, δ): 1.78 (2H, quintet, J=7Hz), 2.65 (2H, t, J=7Hz), 3.18 (2H, t, J=7Hz), 6.88 (1H, d, J=8Hz), 7.22 (1H, s), 7.24 (1H, d, J=8Hz), 7.43

(2H, d, J=8Hz), 7.76 (2H, d, J=8Hz)
(-)ESI-MS (m/z): 402 $(M-H)^-$

(5) Methyl 5-[[4-[[(2R)-2-(formylamino)propyl]oxy]-phenyl]sulfonyl]-2-hydroxybenzoate
NMR ($CDCl_3$, δ): 1.33, 1.35 (total 3H, J=7Hz, a pair of d), 3.90-4.25 (2H, m), 4.00, 3.99 (total 3H, a pair of s), 4.49 (1H, m), 5.76 (1H, br d, J=6Hz), 6.80-7.15 (3H, m), 7.86 (2H, d, J=9Hz), 7.92, 8.11 (total 1H, J=9, 2Hz, a pair of dd), 8.16, 8.23 (total 1H, a pair of br s), 8.46, 8.50 (total 1H, J=2Hz, a pair of d), 11.25, 11.29 (total 1H, a pair of s, OH)
(+)ESI-MS (m/z): 416 $(M+Na)^+$

(6) N-[3-[4-[(3-Chloro-4-methoxyphenyl)sulfonyl]phenyl]-propyl]-2,2,2-trifluoroacetamide
NMR ($CDCl_3$, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 3.94 (3H, s), 6.36 (1H, br s), 7.00 (1H, d, J=9Hz), 7.31 (2H, d, J=8Hz), 7.83 (2H, d, J=8Hz), 7.83 (1H, dd, J=9, 2Hz), 7.91 (1H, d, J=2Hz)
(+)ESI-MS (m/z): 458 $(M+Na)^+$

(7) Methyl 2-hydroxy-5-[[4-[3-[(trifluoroacetyl)amino]-propyl]phenyl]sulfonyl]benzoate
NMR ($CDCl_3$, δ): 1.92 (2H, quintet, J=7Hz), 2.72 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 4.00 (3H, s), 6.33 (1H, br s), 7.07 (1H, d, J=9Hz), 7.31 (2H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 7.95 (1H, dd, J=9 and 2Hz), 8.48 (1H, d, J=2Hz), 11.28 (1H, s, OH)
(+)ESI-MS (m/z): 468 $(M+Na)^+$

Preparation 50

Under nitrogen at room temperature, to a solution of

methyl (4-hydroxyphenyl)acetate (10 g) in N,N-dimethylformamide (50 ml) were added potassium carbonate (9.3 g) and benzyl bromide (8.0 ml), and the mixture was stirred at 60°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with hexane/ethyl acetate (1:1). The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give methyl [4-(benzyloxy)phenyl]acetate (16 g).

NMR ($CDCl_3$, δ): 3.56 (2H, s), 3.68 (3H, s), 5.05 (2H, s), 6.9-7.0 (2H, m), 7.1-7.5 (7H, m)

(+)ESI-MS (m/z): 279 $(M+Na)^+$

Preparation 51

To a solution of methyl [4-(benzyloxy)phenyl]acetate (16 g) in methanol (160 ml) was added 1N sodium hydroxide (68.5 ml) at room temperature, and the mixture was stirred at the same temperature for 2 hours. After removal of methanol under reduced pressure, the residue was dissolved into a mixture of water and ethyl acetate. The aqueous layer was adjusted to pH 2-3 with 6N hydrochloric acid to give deposits. The precipitates were collected and washed with water followed by dryness in vacuo to give [4-(benzyloxy)phenyl]acetic acid (11 g).

NMR (DMSO-d_6, δ): 3.48 (2H, s), 5.08 (2H, s), 6.9-7.0 (2H, m), 7.15-7.2 (2H, m), 7.25-7.5 (5H, m)

(-)ESI-MS (m/z): 241 $(M-H)^-$

Preparation 52

Under nitrogen, to a suspension of [4-(benzyloxy)-phenyl]acetic acid (10.8 g) in dichloromethane (300 ml) were added concentrated sulfuric acid (0.5 ml) and the excess amount of isobutene in dryice-acetone bath, and the mixture was raised to room temperature slowly followed by being

stirred at the same temperature for 3.5 days. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate two times and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1) to give tert-butyl [4-(benzyloxy)phenyl]acetate (11.3 g).

NMR ($CDCl_3$, δ): 1.43 (9H, s), 3.46 (2H, s), 5.05 (2H, s), 6.9-6.95 (2H, m), 7.15-7.5 (7H, m)

(+)ESI-MS (m/z): 321 $(M+Na)^+$

Preparation 53

A mixture of tert-butyl [4-(benzyloxy)phenyl]acetate (11.3 g) and 10% palladium on activated carbon (50% wet, 550 mg) in methanol (110 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 5.5 hours. After filtration, the filtrate was evaporated under reduced pressure and dried in vacuo to give tert-butyl (4-hydroxyphenyl)acetate (8.56 g).

NMR ($CDCl_3$, δ): 1.44 (9H, s), 3.45 (2H, s), 6.7-6.9 (2H, m), 7.05-7.15 (2H, m)

(+)ESI-MS (m/z): 231 $(M+Na)^+$

Preparation 54

Under nitrogen at room temperature, to a solution of tert-butyl benzyl[2-[4-[(triisopropylsilyl)thio]phenyl]-ethyl]carbamate (210 mg) in toluene (3 ml) were added tert-butyl [4-[[(trifluoromethyl)sulfonyl]oxy]phenyl]acetate (157 mg), bis(dibenzylideneacetone)palladium(0) (24.2 mg) bis(2-diphenylphosphinophenyl)ether (22.6 mg) and cesium fluoride (70.2 mg), and the mixture was stirred at 80°C for 17 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer

was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1)to give tert-butyl [4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]ethyl]phenyl]thio]phenyl]-acetate (136 mg).

NMR ($CDCl_3$, δ): 1.43 (9H, s), 1.46 (9H, s), 2.65-2.9 (2H, m), 3.25-3.5 (4H, m), 4.3-4.45 (2H, m), 6.95-7.4 (13H, m)

(+)ESI-MS (m/z): 556 $(M+Na)^+$

Preparation 55

Under nitrogen at room temperature, to a solution of tert-butyl [4-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]sulfonyl]phenyl]acetate (725 mg) in dichloromethane (5 ml) was added trifluoroacetic acid (1 ml), and the mixture was stirred at the same temperature for 4 hours. The resulting mixture was evaporated under reduced pressure. Under nitrogen at room temperature, to the residue in ethanol (10 ml) was added 4N hydrogen chloride in 1,4-dioxane (2 ml), and the mixture was stirred at the same temperature overnight. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, the organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give ethyl [4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]phenyl]acetate (573 mg).

NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7.1Hz), 2.75-2.95 (4H, m), 3.65 (2H, s), 3.79 (2H, s), 4.14 (2H, q, J=7.1Hz), 7.15-7.5 (9H, m), 7.8-7.95 (4H, m)

(+)ESI-MS (m/z): 438 $(M+H)^+$

Preparation 56

Under nitrogen at room temperature, to a mixture of

bis(dibenzylideneacetone)palladium(0) (13.1 mg) and bis(2-diphenylphosphinophenyl)ether (13.3 mg) was added toluene (2 ml). After being stirred at the same temperature for 15 minutes, tert-butyl benzyl[2-(4-iodophenyl)ethyl]carbamate (200 mg) in toluene (2 ml), potassium tert-butoxide (61.6 mg) and triisopropylsilanethiol (0.108 ml) were added, and the mixture was stirred at 80°C for 1 hour. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1) to give tert-butyl benzyl[2-4-[(triisopropylsilyl)thio]-phenyl]ethyl carbamate (210 mg).

NMR ($CDCl_3$, δ): 1.07 (18H, d, J=6.3Hz), 1.1-1.3 (3H, m), 1.4-1.6 (9H, m), 2.65-2.85 (2H, m), 3.2-3.45 (2H, m), 4.2-4.35 (2H, m), 6.9-7.45 (9H, m)

Preparation 57

Under nitrogen, a mixture of formic acid (0.828 ml) and acetic anhydride (2.07 ml) was stirred at 5°C for 30 minutes. To this one was added (R)-1-phenoxy-2-propanamine (1.66 g) in dichloromethane (5 ml), and the mixture was stirred at room temperature for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1:1 to 1:2) to give (R)-1-methyl-2-phenoxyethylformamide (147 g).

NMR ($CDCl_3$, δ): 1.3-1.4 (3H, m), 3.8-4.1 (2H, m), 4.35-4.5 (1H, m), 6.8-7.05 (3H, m), 7.2-7.4 (2H, m), 8.17 (1H, s)

(+)ESI-MS (m/z): 202 $(M+Na)^+$

Preparation 58

A mixture of 4-mercaptophenol (16.2 g) in dimethyl sulfoxide (15 ml) was stirred at 80°C for 5 hours. The resulting mixture was poured into a mixture of water and the aqueous mixture was extracted with hexane/ethyl acetate (1:1). After separation, the organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give di(4-hydroxyphenyl)-disulfide (16.54 g).

(-)ESI-MS (m/z): 249 $(M-H)^-$

Preparation 59

Under nitrogen at room temperature, to a solution of N-benzylethanolamine (50 g) in methanol (250 ml) was added ethyl trifluoroacetate (59 ml) dropwise, and the mixture was stirred at 45°C for 2 hours. The resulting mixture was evaporated under reduced pressure. The residue was dissolved into a mixture of 1N hydrochloric acid and hexane/ethyl acetate (1:1). After separation, the organic layer was washed successively with water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and dried in vacuo to give N-benzyl-2,2,2-trifluoro-N-(2-hydroxyethyl)-acetamide (64 g).

(+)ESI-MS (m/z): 270 $(M+Na)^+$

Preparation 60

To a solution of (R)-2-chloro-4-[[4-[2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate (1.0 g) and 3-ethoxycarbonylphenylboronic acid (455 mg) in 1,2-dimethoxyethane (10 ml) were added

tetrakis(triphenylphosphine)palladium(0) (104 mg) and 2M sodium carbonate (1.90 ml) at room temperature, and the mixture was stirred at 80°C for 4 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3:1 to 2:1) to give ethyl (R)-2'-chloro-4'-[[4-[2-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate (783 mg).

NMR ($CDCl_3$, δ): 1.23 (3H, d, J=6.7Hz), 1.39 (3H, t, J=7.1Hz), 2.8-3.1 (2H, m), 4.2-4.5 (3H, m), 7.38 (2H, d, J=8.3Hz), 7.4-7.6 (3H, m), 7.8-8.2 (6H, m)

(+)ESI-MS (m/z): 576 $(M+Na)^+$

Preparation 61

Under nitrogen at room temperature, to a solution of (R)-1-phenoxy-2-propanamine (1.4 g) in methanol (7 ml) was added ethyl trifluoroacetate (1.32 ml) dropwise, and the mixture was stirred at the same temperature overnight. The resulting mixture was evaporated under reduced pressure and dried in vacuo to give (R)-2,2,2-trifluoro-N-(1-methyl-2-phenoxyethyl)acetamide (2.13 g).

NMR ($CDCl_3$, δ): 1.41 (3H, d, J=6.9Hz), 3.9-4.1 (2H, m), 4.3-4.55 (1H, m), 6.85-7.05 (3H, m), 7.2-7.4 (2H, m)

(+)ESI-MS (m/z): 270 $(M+Na)^+$

Preparation 62

To a solution of 2,2,2-trifluoro-N-[3-[4-[(3-methoxyphenyl)sulfonyl]phenyl]propyl]acetamide (6.13 g) in 1,4-dioxane (61 ml) was added 1N sodium hydroxide solution (23 ml), and the mixture was stirred at room temperature for 12 hours. After being concentrated, the mixture was

partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give 3-[4-[(3-methoxyphenyl)sulfonyl]phenyl]propylamine (3.46 g) as a pale yellow oil.

NMR ($CDCl_3$, δ): 1.76 (2H, quintet, J=7Hz), 2.60-2.82 (4H, m), 3.84 (3H, s), 7.01-7.13 (1H, m), 7.20-7.55 (5H, m), 7.85 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 306 $(M+H)^+$

Preparation 63

Under nitrogen atmosphere, to an ice-cooled solution of 4-iodophenol (15.40 g), triphenylphosphine (22.03 g), and tert-butyl benzyl(2-hydroxyethyl)carbamate (21.05 g) in tetrahydrofuran (123 ml) was added diethyl azodicarboxylate (14.58 g) in tetrahydrofuran (31 ml) for 25 minutes, and the mixture was stirred at room temperature for 2 hours. After being concentrated, the mixture was treated with hexane/ethyl acetate (5/1, 180 ml). The precipitate formed was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give tert-butyl benzyl[2-(4-iodophenoxy)ethyl]carbamate (7.17 g) as a colorless oil.

NMR ($CDCl_3$, δ): 1.45 (9H, s), 3.58 (2H, br s), 4.07 (2H, br s), 4.55 (2H, s), 6.62 (2H, d, J=8Hz), 7.10-7.40 (5H, m), 7.53 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 476 $(M+Na)^+$

Preparation 64

To a solution of N-[2-[4-[[4-[2-[benzyl(2,2,2-trifluoroacetyl)amino]ethoxy]phenyl]dithio]phenoxy]ethyl]-N-benzyl-2,2,2-trifluoroacetamide (359 mg) in ethanol/tetrahydrofuran (2/1, 5.4 ml) was added triphenylphosphine (142 mg), and the mixture was stirred at room temperature for 6 hours. The mixture was partitioned

between ethyl acetate and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give N-benzyl-2,2,2-trifluoro-N-[2-(4-mercaptophenoxy)ethyl]acetamide (525 mg) as a colorless oil.

NMR ($CDCl_3$, δ): 3.37 (1H, s), 3.55-3.85 (2H, m), 4.00-4.20 (2H, m), 4.80, 4.84 (total 2H, a pair of s), 6.75 (2H, d, J=9Hz), 7.05-7.85 (7H, m)

(-)APCI-MS (m/z): 354 $(M-H)^-$

Preparation 65

To a solution of methyl 5-iodosalicylate (5.56 g) in N,N-dimethylformamide (56 ml) were added powdered potassium carbonate (3.04 g) and benzyl bromide (2.6 ml), and the mixture was stirred at room temperature for 45 hours. The mixture was partitioned between hexane/ethyl acetate (1/2) and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The solvent was evaporated to give methyl 2-benzyloxy-5-iodobenzoate (8.07 g) as a pale yellow oil.

NMR ($CDCl_3$, δ): 3.90 (3H, s), 5.17 (2H, s), 6.78 (1H, d, J=9Hz), 7.26-7.52 (5H, m), 7.69 (1H, dd, J=9, 2Hz), 8.10 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 391 $(M+Na)^+$

Preparation 66

Chlorosulfonic acid (10 ml) was cooled in an ice bath whereupon methyl salicylate (7.60 g) was added dropwise over 20 minutes. The mixture was heated to 40°C for 30 minutes, allowed to cool to room temperature, and poured onto crashed ice. The precipitate formed was collected, washed with water, and dried in vacuo to give methyl 5-chlorosulfonyl-2-hydroxybenzoate (7.89 g) as a white powder.

NMR ($CDCl_3$, δ): 4.04 (3H, s), 7.18 (1H, d, J=9Hz), 8.09

(1H, dd, J=9, 2Hz), 8.57 (1H, d, J=2Hz), 11.55 (1H, s, OH)

Preparation 67

Methyl 5-[[4-[[(2R)-2-(formylamino)propyl]oxy]phenyl]-sulfonyl]-2-hydroxybenzoate (1.60 g) and hydrogen chloride in methanol (10-20%, 16 ml) were mixed and stirred at room temperature for 12 hours. The solvent was evaporated to give methyl 5-[[4-[[(2R)-2-aminopropyl]oxy]phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride (1.67 g) as a white solid.

NMR (DMSO-d_6, δ): 1.28 (3H, d, J=7Hz), 3.35-3.75 (1H, m), 3.89 (3H, s), 3.92-4.32 (2H, m), 7.18 (1H, d, J=9Hz), 7.19 (2H, d, J=9Hz), 7.90 (2H, d, J=9Hz), 7.97 (1H, dd, J=9, 2Hz), 8.21 (1H, d, J=2Hz), 11.27 (1H, s, OH)

(+)ESI-MS (m/z): 366 (free, $M+H)^+$

Preparation 68

To a solution of methyl 2-hydroxy-5-[[4-[3-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]benzoate (4.43 g) in N,N-dimethylformamide (35 ml) were added powdered potassium carbonate (2.73 g) and iodomethane (0.93 ml), and the mixture was stirred at 50°C for 2 hours. After being allowed to cool to room temperature, the mixture was partitioned between hexane/ethyl acetate (1/2) and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give methyl 2-methoxy-5-[[4-[3-[(trifluoroacetyl)amino]propyl]phenyl]sulfonyl]-benzoate (4.81 g) as a pale yellow solid.

NMR ($CDCl_3$, δ): 1.92 (2H, quintet, J=7Hz), 2.68 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 3.86 (3H, s), 3.95 (3H, s), 6.40 (1H, br s), 7.06 (1H, d, J=9Hz), 7.31 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz), 8.03 (1H, dd, J=9, 2Hz), 8.34 (1H, d, J=2Hz)

(-)ESI-MS (m/z): 458 $(M-H)^-$

Preparation 69

The following compounds were obtained according to a similar manner to that of Preparation 22.

(1) (R)-2,2,2-Trifluoro-N-[2-[4-[(3-methoxyphenyl)thio]-phenyl]-1-methylethyl]acetamide
NMR ($CDCl_3$, δ): 1.22 (3H, d, J=6.7Hz), 2.7-2.95 (2H, m), 3.75 (3H, s), 4.2-4.35 (1H, m), 6.7-6.95 (3H, m), 7.05-7.35 (5H, m)
(+)ESI-MS (m/z): 392 $(M+Na)^+$

(2) 2,2,2-Trifluoro-N-[3-[4-[(3-methoxyphenyl)thio]-phenyl]propyl]acetamide
NMR ($CDCl_3$, δ): 1.92 (2H, quintet, J=7Hz), 2.67 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 3.76 (3H, s), 6.25 (1H, br s), 6.65-6.95 (3H, m), 7.13 (2H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.32 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 392 $(M+Na)^+$

(3) tert-Butyl benzyl[2-[4-[(4-hydroxyphenyl)thio]-phenoxy]ethyl]carbamate
NMR ($CDCl_3$, δ): 1.45 (9H, s), 3.58 (2H, br s), 4.07 (2H, br s), 4.55 (2H, s), 5.20 (1H, br s, OH), 6.77 (4H, d, J=8Hz), 7.10-7.42 (9H, m)
(+)ESI-MS (m/z): 474 $(M+Na)^+$

(4) Methyl 2-benzyloxy-5-[[4-[2-[benzyl(trifluoroacetyl)-amino]ethoxy]phenyl]thio]benzoate
NMR ($CDCl_3$, δ): 3.60-3.83 (2H, m), 3.88 (3H, s), 4.02-4.22 (2H, m), 4.81, 4.85 (total 2H, a pair of s), 5.16 (2H, s), 6.80 (2H, d, J=9Hz), 6.93 (1H, d, J=9Hz), 7.15-7.55 (13H, m), 7.80 (1H, d, J=2Hz)
(+)ESI-MS (m/z): 618 $(M+Na)^+$

Preparation 70

The following compounds were obtained according to a similar manner to that of Preparation 24.

(1) Ethyl (R)-3-[3-[[4-[2-[(trifluoroacetyl)amino]propyl]-phenyl]thio]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.21 (3H, d, J=6.6Hz), 1.39 (3H, t, J=7.3Hz), 2.7-2.95 (2H, m), 4.2-4.45 (3H, m), 6.75-7.85 (12H, m)

(+)ESI-MS (m/z): 526 $(M+Na)^+$

(2) Ethyl 4-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]thio]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.2Hz), 1.4-1.55 (9H, m), 2.7-2.9 (2H, m), 3.3-3.5 (2H, m), 4.3-4.5 (4H, m), 6.8-7.4 (15H, m), 7.95-8.0 (2H, m)

(+)ESI-MS (m/z): 606 $(M+Na)^+$

(3) Ethyl 3-[3-[[4-[2-[benzyl(tert-butoxycarbonyl)amino]-ethyl]phenyl]thio]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.39 (3H, t, J=7.2Hz), 1.4-1.55 (9H, m), 2.65-2.85 (2H, m), 3.25-3.5 (2H, m), 4.3-4.5 (4H, m), 6.75-7.4 (15H, m), 7.64 (1H, m), 7.76 (1H, m)

(+)ESI-MS (m/z): 606 $(M+Na)^+$

Preparation 71

The following compound was obtained according to a similar manner to that of Preparation 48.

(R)-4-[2-[(Trifluoroacetyl)amino]propyl]benzenesulfonyl chloride

NMR ($CDCl_3$, δ): 1.27 (3H, d, J=6.7Hz), 2.92 (1H, dd, J=7.3, 13.6Hz), 3.07 (1H, dd, J=6.1, 13.6Hz), 4.32 (1H, h, J=7.0Hz), 6.19 (1H, br), 7.44 (2H, d,

J=8.5Hz), 8.00 (2H, d, J=8.5Hz)

Preparation 72

The following compounds were obtained according to a similar manner to that of Preparation 60.

(1) Ethyl (R)-3'-[[4-[2-[(trifluoroacetyl)amino]propyl]-phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.21 (3H, d, J=6.7Hz), 1.42 (3H, t, J=7.1Hz), 2.75-3.05 (2H, m), 4.15-4.35 (1H, m), 4.43 (2H, q, J=7.1Hz), 7.33 (2H, d, J=8.3Hz), 7.45-8.3 (10H, m)
(+)ESI-MS (m/z): 542 $(M+Na)^+$

(2) Ethyl 2'-(methoxymethoxy)-4'-[[4-[2-[(trifluoroacetyl)-amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.26 (3H, t, J=7.1Hz), 2.97 (2H, t, J=7.1Hz), 3.93 (3H, s), 2.6-2.65 (2H, m), 4.38 (2H, q, J=7.1Hz), 5.18 (2H, s), 7.36 (2H, d, J=8.4Hz), 7.45-7.55 (2H, m), 7.6-7.7 (2H, m), 7.76 (1H, m), 7.96 (2H, d, J=8.4Hz), 8.05 (1H, d, J=7.8Hz), 8.15 (1H, m)
(+)ESI-MS (m/z): 588 $(M+Na)^+$

Preparation 73

The following compound was obtained according to a similar manner to that of Preparation 21.

2,2,2-Trifluoro-N-[3-(4-iodophenyl)propyl]acetamide
NMR ($CDCl_3$, δ): 1.90 (2H, quintet, J=7Hz), 2.62 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 6.26 (1H, br s), 6.93 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 380 $(M+Na)^+$

Preparation 74

The following compound was obtained according to a similar manner to that of Preparation 62.

(1R)-2-[4-[(2-Methoxyphenyl)sulfonyl]phenyl]-1-methylethylamine

NMR ($CDCl_3$, δ): 1.12 (3H, d, J=6Hz), 2.62 (1H, dd, J=13, 8Hz), 2.75 (1H, dd, J=13, 6Hz), 3.08-3.34 (1H, m), 3.77 (3H, s), 6.91 (1H, d, J=8Hz), 7.10 (1H, t, J=8Hz), 7.30 (2H, d, J=8Hz), 7.44-7.64 (1H, m), 7.90 (2H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 306 $(M+H)^+$

Preparation 75

The following compound was obtained according to a similar manner to that of Preparation 9.

N-[3-[4-[[4-(Benzyloxy)-3-hydroxyphenyl]sulfonyl]-phenyl]propyl]-2,2,2-trifluoroacetamide

NMR ($CDCl_3$, δ): 1.89 (2H, quintet, J=7Hz), 2.69 (2H, t, J=7Hz), 3.36 (2H, q, J=7Hz), 5.14 (2H, s), 5.93 (1H, s, OH), 6.60 (1H, br s), 6.97 (1H, d, J=8Hz), 7.15-7.60 (9H, m), 7.80 (2H, d, J=8Hz)

(-)ESI-MS (m/z): 492 $(M-H)^-$

Preparation 76

The following compound was obtained according to a similar manner to that of Preparation 15.

N-[3-[4-[[4-Benzyloxy-3-(methoxymethoxy)phenyl]-sulfonyl]phenyl]propyl]-2,2,2-trifluoroacetamide

NMR ($CDCl_3$, δ): 1.95 (2H, quintet, J=7Hz), 2.71 (2H, t, J=7Hz), 3.37 (2H, q, J=7Hz), 3.50 (3H, s), 5.17 (2H, s), 5.24 (2H, s), 6.34 (1H, br s), 6.96 (1H, d, J=9Hz), 7.16-7.50 (7H, m), 7.54 (1H, dd, J=9,

2Hz), 7.67 (1H, d, J=2Hz), 7.83 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 560 $(M+Na)^+$

Preparation 77

The following compound was obtained according to a similar manner to that of Preparation 63.

N-[2-[4-[[4-[2-[Benzyl(2,2,2-trifluoroacetyl)amino]-ethoxy]phenyl]dithio]phenoxy]ethyl]-N-benzyl-2,2,2-trifluoroacetamide

NMR ($CDCl_3$, δ): 3.55-3.85 (4H, m), 4.00-4.25 (4H, m), 4.80, 4.84 (total 4H, a pair of s), 6.79 (4H, d, J=8Hz), 7.10-7.50 (14H, m)
(+)ESI-MS (m/z): 731 $(M+Na)^+$

Example 1

Under nitrogen at room temperature, to a solution of methyl 4-[[4-(2-aminoethyl)phenyl]sulfonyl]-2-pyridinecarboxylate (335 mg) in dimethylsulfoxide (5 ml) was added N,O-bis(trimethylsilyl)acetamide (0.127 ml), and the mixture was stirred at the same temperature for 1 hour. To this one was added (R)-2-(3-chlorophenyl)oxirane (194 mg) and the mixture was stirred at 80°C for 20 hours. The resulting mixture was cooled to room temperature and 10% aqueous acetic acid was added. After being stirred for 20 minutes, the mixture was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with chloroform. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1 to 15:1) to give methyl (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]-2-pyridinecarboxylate (158 mg).

NMR ($CDCl_3$, δ): 2.6-3.1 (6H, m), 4.03 (3H, s), 4.6-4.7

(1H, m), 7.15-8.05 (8H, m), 8.45-8.75 (2H, m), 8.95 (1H, d, J=5.0Hz)

(+)ESI-MS (m/z): 475, 477 $(M+H)^+$

Example 2

To a suspension of methyl (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-pyridinecarboxylate (155 mg) in a mixture of ethanol (3 ml) and tetrahydrofuran (1.5 ml) was added 1N sodium hydroxide (0.326 ml) at room temperature, and the mixture was stirred at the same temperature for 3.5 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by reversed phase chromatography to give sodium (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenyl]sulfonyl]-2-pyridinecarboxylate (3.9 mg).

NMR (DMSO-d_6, δ): 2.55-2.85 (6H, m), 4.5-4.65 (1H, m), 7.2-7.35 (4H, m), 7.48 (2H, d, J=8.3Hz), 7.75-7.8 (1H, m), 7.87 (2H, d, J=8.3Hz), 8.15 (1H, br s), 8.72 (1H, d, J=5.0Hz)

(-)ESI-MS (m/z): 459, 461 $(M-Na)^-$

Example 3

The following compounds were obtained according to a similar manner to that of Example 6.

(1) Ethyl 5-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR ($CDCl_3$, δ): 1.45 (3H, t, J=7Hz), 2.45-3.00 (6H, m), 3.54 (1H, d, J=13Hz), 3.63 (1H, br s, OH), 3.90 (1H, d, J=13Hz), 4.45 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05 (1H, d, J=9Hz), 7.05-7.40 (11H, m), 7.80 (2H, d, J=8Hz), 7.92 (1H, dd, J=9, 2Hz), 8.49 (1H, d, J=2Hz), 11.40 (1H, s, OH)

(+)ESI-MS (m/z): 594 $(M+H)^+$

(2) Ethyl 3-[4-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.06 (3H, d, J=6.2Hz), 1.37 (3H, t, J=7.1Hz), 2.6-3.0 (5H, m), 4.37 (2H, q, J=7.1Hz), 4.55 (1H, dd, J=3.8, 8.5Hz), 6.95-7.1 (2H, m), 7.1-7.55 (8H, m), 7.7 (1H, m), 7.8-7.95 (5H, m)

(+)ESI-MS (m/z): 594, 596 $(M+H)^+$

(3) Ethyl (R)-2-[4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.06 (3H, t, J=7.1Hz), 2.5-2.95 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.91 (1H, d, J=13.4Hz), 4.16 (2H, q, J=7.1Hz), 4.62 (1H, dd, J=3.5, 9.8Hz), 6.85-7.35 (15H, m), 7.5-7.6 (1H, m), 7.7-8.0 (5H, m)

(+)ESI-MS (m/z): 670, 672 $(M+H)^+$

(4) Ethyl (R)-2-[3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.06 (3H, t, J=7.1Hz), 2.5-2.95 (6H, m), 3.56 (1H, d, J=13.4Hz), 3.92 (1H, d, J=13.4Hz), 4.15 (2H, d, J=7.1Hz), 4.62 (1H, dd, J=3.7, 9.8Hz), 6.95-7.6 (18H, m), 7.75-7.85 (2H, m), 7.9-8.0 (1H, m)

(+)ESI-MS (m/z): 670 $(M+H)^+$

(5) Ethyl (R)-[4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl]acetate

NMR ($CDCl_3$, δ): 1.25 (3H, t, J=7.3Hz), 2.52.95 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.64 (2H, s), 3.90 (1H, d, J=13.4Hz), 4.12 (2H, t, J=7.3Hz), 4.61 (1H, dd,

J=3.7, 9.8Hz), 7.1-7.35 (11H, m), 7.41 (2H, d, J=8.3Hz), 7.75-7.95 (4H, m)
(+)ESI-MS (m/z): 592, 594 $(M+H)^+$

(6) (R)-4-[[4-[2-[Benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonylphenol
NMR ($CDCl_3$, δ): 2.5-2.95 (6H, m), 3.5-3.95 (2H, m), 4.55-4.65 (1H, m), 6.85-6.95 (2H, m), 7.1-7.4 (11H, m), 7.75-7.9 (4H, m)
(+)ESI-MS (m/z): 522, 524 $(M+H)^+$

(7) Ethyl 3-[3-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate
NMR ($CDCl_3$, δ): 1.07 (3H, d, J=6.2Hz), 1.38 (3H, t, J=7.2Hz), 2.6-3.0 (5H, m), 4.37 (2H, q, J=7.2Hz), 4.5-4.6 (1H, m), 7.1-7.7 (13H, m), 7.8-7.9 (3H, m)
(+)APCI-MS (m/z): 594 $(M+H)^+$

(8) Ethyl 4'-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.06 (3H, d, J=6.1Hz), 1.44 (3H, t, J=7.1Hz), 2.6-3.0 (5H, m), 4.41 (2H, q, J=7.1Hz), 7.1-7.35 (6H, m), 7.55 (1H, t, J=7.7Hz), 7.65-8.1 (8H, m), 8.2-8.25 (1H, m)
(+)ESI-MS (m/z): 578, 580 $(M+H)^+$

(9) Ethyl 3'-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.05 (3H, d, J=6.1Hz), 1.42 (3H, t, J=7.2Hz), 2.55-3.0 (5H, m), 4.42 (2H, q, J=7.2Hz), 4.45-4.55 (1H, m), 7.1-7.35 (6H, m), 7.45-7.65 (2H, m), 7.7-8.3 (8H, m)

(+)ESI-MS (m/z): 578 $(M+H)^+$

(10) (R)-3-[[4-[2-[Benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol

NMR ($CDCl_3$, δ): 2.45-3.0 (6H, m), 3.5-4.0 (2H, m), 4.45-4.55 (1H, m), 6.9-7.45 (14H, m), 7.5-7.55 (1H, m), 7.8-7.9 (2H, m)

(+)APCI-MS (m/z): 522, 524 $(M+H)^+$

(11) Ethyl (R)-3-[3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.1Hz), 2.5-2.95 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.91 (1H, d, J=13.4Hz), 4.37 (2H, q, J=7.1Hz), 7.1-7.5 (15H, m), 7.55-7.7 (3H, m), 7.75-7.9 (3H, m)

(+)ESI-MS (m/z): 670, 672 $(M+H)^+$

(12) Ethyl 5-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methoxybenzoate

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7Hz), 1.82 (2H, quintet, J=7Hz), 2.55-3.00 (6H, m), 3.93 (3H, s), 4.36 (2H, q, J=7Hz), 4.69 (1H, dd, J=9, 4Hz), 7.04 (1H, d, J=9Hz), 7.10-7.45 (6H, m), 7.83 (2H, d, J=8Hz), 8.02 (1H, dd, J=9, 2Hz), 8.32 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 532 $(M+H)^+$

(13) Ethyl (R)-4-[3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.39 (3H, t, J=7.1Hz), 2.55-2.95 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.91 (1H, d, J=13.4Hz), 4.38 (2H, q, J=7.1Hz), 4.61 (1H, dd, J=3.6, 9.8Hz), 6.95-7.05 (2H, m), 7.1-7.35 (12H, m), 7.4-7.75 (3H,

m), 7.80 (2H, d, J=8.2Hz), 8.0-8.1 (2H, m)
(+)ESI-MS (m/z): 670, 672 $(M+H)^+$

(14) Ethyl 4'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.1Hz), 2.45-3.0 (6H, m), 3.54 (1H, d, J=13.4Hz), 3.92 (1H, d, J=13.4Hz), 4.38 (2H, q, J=7.1Hz), 4.53 (1H, dd, J=3.8, 9.9Hz), 7.0-7.7 (16H, m), 7.90 (2H, d, J=8.3Hz), 8.0-8.2 (2H, m)
(+)ESI-MS (m/z): 670, 672 $(M+H)^+$

(15) Ethyl 4-[[4-[[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]benzoate
NMR ($CDCl_3$, δ): 1.19 (3H, d, J=6.5Hz), 1.39 (3H, t, J=7.1Hz), 2.71 (1H, dd, J=9.0, 12.2Hz), 2.97 (1H, dd, J=3.7, 12.2Hz), 3.05-3.2 (1H, m), 3.8-4.0 (2H, m), 4.39 (2H, q, J=7.1Hz), 4.63 (1H, dd, J=3.6, 8.9Hz), 6.9-7.0 (2H, m), 7.15-7.4 (4H, m), 7.8-8.0 (4H, m), 8.1-8.2 (2H, m)
(+)ESI-MS (m/z): 518, 520 $(M+H)^+$

(16) 3-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenol
NMR ($CDCl_3$, δ): 1.81 (2H, quintet, J=7Hz), 2.35-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.86 (1H, d, J=13Hz), 4.59 (1H, dd, J=10, 4Hz), 6.90-7.60 (15H, m), 7.80 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 536 $(M+H)^+$

(17) 4-[[4-[2-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenol
NMR ($CDCl_3$, δ): 2.65 (1H, dd, J=13, 10Hz), 2.82-3.22 (2H, m), 2.85 (1H, dd, J=13, 4Hz), 3.69 (1H, d,

J=13Hz), 3.86-4.18 (2H, m), 3.94 (1H, d, J=13Hz), 4.64 (1H, dd, J=10, 3Hz), 6.85 (2H, d, J=8Hz), 6.91 (2H, d, J=8Hz), 7.05-7.40 (9H, m), 7.76 (2H, d, J=8Hz), 7.81 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 538 $(M+H)^+$

(18) 2-[[4-[(2R)-2-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenol

NMR ($CDCl_3$, δ): 1.03 (3H, d, J=6Hz), 2.40-2.90 (4H, m), 3.00-3.25 (1H, m), 3.47 (1H, d, J=13Hz), 3.56 (1H, br s, OH), 3.80 (1H, d, J=13Hz), 4.56 (1H, dd, J=10, 4Hz), 6.85-7.55 (14H, m), 7.66 (1H, t, J=8Hz), 7.77 (2H, d, J=8Hz), 9.23 (1H, br s)

(-)ESI-MS (m/z): 534 $(M-H)^-$

(19) Ethyl 5-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR ($CDCl_3$, δ): 1.45 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.32-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 3.90 (1H, br s, OH),4.46 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05 (1H, d, J=9Hz), 7.05-7.45 (11H, m), 7.80 (2H, d, J=8Hz), 7.93 (1H, dd, J=9, 2Hz), 8.49 (1H, d, J=2Hz), 11.40 (1H, s, OH)

(20) Ethyl 4-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.32-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 3.88 (1H, br s, OH), 4.43 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05-7.45 (11H, m), 7.41 (1H, dd, J=8, 2Hz), 7.51 (1H, d, J=2Hz), 7.82 (2H, d, J=8Hz), 7.96 (1H, d,

J=8Hz), 11.01 (1H, s, OH)
(+)ESI-MS (m/z): 608 $(M+H)^+$

(21) Ethyl 5-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-2-hydroxybenzoate
NMR ($CDCl_3$, δ): 1.49 (3H, t, J=7Hz), 2.64 (1H, dd, J=13, 10Hz), 2.83-3.20 (2H, m), 2.85 (1H, dd, J=13, 4Hz), 3.69 (1H, d, J=13Hz), 3.90-4.10 (2H, m), 3.94 (1H, d, J=13Hz), 4.46 (2H, q, J=7Hz), 4.64 (1H, dd, J=10, 4Hz), 6.93 (2H, d, J=9Hz), 7.05 (1H, d, J=9Hz), 7.10-7.38 (9H, m), 7.85 (2H, d, J=9Hz), 7.92 (1H, dd, J=9, 2Hz), 8.47 (1H, d, J=2Hz), 11.38 (1H, s, OH)
(+)ESI-MS (m/z): 610 $(M+H)^+$

(22) Ethyl 5-[[4-[[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]-2-hydroxybenzoate
NMR ($CDCl_3$, δ): 1.19 (3H, d, J=6Hz), 1.45 (3H, t, J=7Hz), 2.70 (1H, dd, J=12, 9Hz), 2.97 (1H, dd, J=12, 4Hz), 3.00-3.25 (1H, m), 3.72-4.00 (2H, m), 4.45 (2H, q, J=7Hz), 4.63 (1H, dd, J=9, 4Hz), 6.96 (2H, d, J=9Hz), 7.05 (1H, d, J=9Hz), 7.12-7.45 (4H, m), 7.86 (2H, d, J=9Hz), 7.91 (1H, dd, J=9, 2Hz), 8.46 (1H, d, J=2Hz)
(-)ESI-MS (m/z): 532 $(M-H)^-$

(23) Ethyl 2-chloro-4-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate
NMR ($CDCl_3$, δ): 1.39 (3H, t, J=7Hz), 1.94 (2H, quintet, J=7Hz), 2.60-3.10 (6H, m), 4.40 (2H, q, J=7Hz), 4.89 (1H, dd, J=9, 4Hz), 7.10-7.45 (6H, m), 7.70-7.97 (4H, m), 7.99 (1H, s)
(+)ESI-MS (m/z): 536 $(M+H)^+$

Example 4

The following compound was obtained according to a similar manner to that of Example 23.

Ethyl 5-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride

NMR (DMSO-d_6, δ): 1.34 (3H, t, J=7Hz), 2.92-3.32 (6H, m), 4.37 (2H, q, J=7Hz), 4.98 (1H, m), 6.33 (1H, br s, OH), 7.19 (1H, d, J=9Hz), 7.25-7.60 (6H, m), 7.91 (2H, d, J=8Hz), 8.00 (1H, dd, J=9, 2Hz), 8.23 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 504 (free, $M+H)^+$

Example 5

The following compounds were obtained according to a similar manner to that of Example 8.

(1) Sodium [4-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate

NMR (DMSO-d_6, δ): 2.50-2.85 (6H, m), 4.60 (1H, m), 5.39 (1H, br s, OH), 6.72 (1H, d, J=9Hz), 7.12-7.50 (6H, m), 7.65 (1H, dd, J=9, 2Hz), 7.73 (2H, d, J=8Hz), 8.13 (1H, d, J=2Hz), 18.20 (1H, br s, OH)

(-)ESI-MS (m/z): 474 (free, $M-H)^-$

(2) Sodium (R)-2-[4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 2.65-2.85 (6H, m), 4.5-4.65 (2H, m), 6.8-6.95 (3H, m), 7.1-7.6 (9H, m), 7.75-7.9 (4H, m)

(-)ESI-MS (m/z): 550, 552 $(M-Na)^-$

(3) Sodium 3-[4-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 0.90 (3H, d, J=5.9Hz), 2.4-2.95 (5H, m), 4.45-4.55 (1H, m), 6.95-7.5 (11H, m), 7.65-7.95 (5H, m)

(-)ESI-MS (m/z): 564, 566 $(M-Na)^-$

(4) Sodium (R)-2-[3-[[4-(2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl)phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 2.55-2.85 (6H, m), 4.55-4.7 (1H, m), 6.85-7.6 (14H, m), 7.80 (2H, d, J=8.2Hz)

(-)ESI-MS (m/z): 550, 552 $(M-Na)^-$

(5) Sodium 5-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (DMSO-d_6, δ): 1.06 (3H, d, J=6.2Hz), 2.6-3.3 (5H, m), 4.8-4.95 (1H, m), 6.74 (1H, d, J=8.8Hz), 7.25-7.55 (6H, m), 7.68 (1H, dd, J=2.6, 8.6Hz), 7.82 (2H, d, J=8.3Hz), 8.15 (1H, m)

(-)ESI-MS (m/z): 488, 490 $(M-Na)^-$

(6) Sodium 3-[3-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 1.04 (3H, d, J=6.1Hz), 2.4-2.9 (5H, m), 4.5-4.6 (1H, m), 7.0-7.05 (1H, m), 7.2-7.9 (15H, m)

(-)ESI-MS (m/z): 564, 566 $(M-Na)^-$

(7) Sodium 4'-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-

biphenyl-3-carboxylate
NMR (DMSO-d_6, δ): 0.92 (3H, d, J=5.9Hz), 2.4-2.95 (5H, m), 4.55-4.65 (1H, m), 7.2-7.55 (7H, m), 7.75-8.1 (8H, m), 8.2 (1H, m)
(-)ESI-MS (m/z): 548, 550 $(M-Na)^-$

(8) Sodium 3'-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR (DMSO-d_6, δ): 0.89 (3H, d, J=5.9Hz), 2.5-2.9 (5H, m), 4.5-4.9 (1H, m), 7.15-7.45 (7H, m), 7.55-7.75 (2H, m), 7.85-8.0 (5H, m), 8.1-8.15 (2H, m)
(-)ESI-MS (m/z): 548, 550 $(M-Na)^-$

(9) Sodium (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate
NMR (DMSO-d_6, δ): 2.55-2.9 (6H, m), 4.55-4.65 (1H, m), 7.2-7.5 (6H, m), 7.6-7.8 (3H, m), 7.85-8.1 (6H, m), 8.18 (1H, m)
(-)ESI-MS (m/z): 535 $(M-Na)^-$

(10) Sodium (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR (DMSO-d_6, δ): 2.5-2.8 (6H, m), 4.5-4.6 (1H, m), 7.2-7.5 (7H, m), 7.6-7.8 (2H, m), 7.85-8.0 (5H, m), 8.1-8.15 (2H, m)
(-)ESI-MS (m/z): 534 $(M-Na)^-$

(11) Sodium (R)-3'-[[4-(2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl)phenyl]sulfonyl]-1,1'-biphenyl-2-carboxylate
NMR (DMSO-d_6, δ): 2.5-2.9 (6H, m), 4.55-4.7 (1H, m), 7.15-8.0 (16H, m)

(-)ESI-MS (m/z): 534, 536 $(M-Na)^-$

(12) Sodium (R)-4-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 2.5-2.9 (6H, m), 4.45-4.6 (1H, m), 6.85-7.0 (2H, m), 7.15-7.5 (8H, m), 7.5-7.7 (2H, m), 7.7-8.0 (4H, m)

(-)ESI-MS (m/z): 550, 552 $(M-Na)^-$

(13) Sodium (R)-3-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 2.55-2.85 (6H, m), 4.55-4.7 (1H, m), 7.0-7.1 (1H, m), 7.2-7.5 (10H, m), 7.55-7.9 (5H, m)

(-)ESI-MS (m/z): 550, 552 $(M-Na)^-$

(14) Sodium (R)-4'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate

NMR (DMSO-d_6, δ): 2.4-3.0 (6H, m), 4.2-4.4 (1H, m), 7.2-7.65 (11H, m), 7.75-7.9 (3H, m), 8.07 (1H, m)

(-)ESI-MS (m/z): 550, 552 $(M-Na)^-$

(15) Sodium [3-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate

NMR (DMSO-d_6, δ): 1.67 (2H, quintet, J=7Hz), 2.40-2.80 (6H, m), 4.17 (2H, s), 4.60 (1H, m), 5.51 (1H, br s, OH), 6.92-7.60 (1H, m), 7.82 (2H, d, J=8Hz)

(-)ESI-MS (m/z): 502 (free, $M-H)^-$

(16) Sodium 3-[[4-[3-[[(2R)-2-(3-chlorphenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate

NMR (DMSO-d_6, δ): 1.66 (2H, quintet, J=7Hz), 2.40-2.80 (6H, m), 4.60 (1H, m), 5.44 (1H, br s, OH), 7.15-7.60 (7H, m), 7.72-7.92 (3H, m), 8.07 (1H, d, J=8Hz), 8.30 (1H, s)

(-)ESI-MS (m/z): 472 (free, $M-H)^-$

(17) Sodium [4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenoxy]-acetate

NMR (DMSO-d_6, δ): 2.55-3.00 (4H, m), 4.08 (2H, m), 4.20 (2H, s), 4.63 (1H, m), 5.50 (1H, br s, OH), 6.93 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.15-7.45 (4H, m), 7.75 (2H, d, J=8Hz), 7.80 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 504 (free, $M+H)^+$

(18) Sodium 4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]benzoate

NMR (DMSO-d_6, δ): 2.58-3.00 (4H, m), 4.08 (2H, m), 4.63 (1H, m), 5.47 (1H, br s, OH), 7.11 (2H, d, J=8Hz), 7.20-7.45 (4H, m), 7.79 (2H, d, J=8Hz), 7.84 (2H, d, J=8Hz), 7.98 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 474 (free, $M+H)^+$

(19) Sodium [2-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate

NMR (DMSO-d_6, δ): 0.93 (3H, d, J=6Hz), 2.40-3.10 (5H, m), 4.03 (2H, s), 4.54 (1H, m), 6.04 (1H, br s, OH), 6.82-7.62 (9H, m), 7.78-8.05 (3H, m)

(-)ESI-MS (m/z): 502 (free, $M-H)^-$

(20) Sodium 2-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl[phenyl]sulfonyl]benzoate

NMR (DMSO-d_6, δ): 0.74 (3H, d, J=6Hz), 2.50-3.20 (5H, m), 4.72 (1H, m), 7.10-7.60 (9H, m), 7.80-8.15 (3H,

m)
(-)ESI-MS (m/z): 472 (free, $M-H)^-$

(21) Sodium 4'-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR (DMSO-d_6, δ): 2.58-3.02 (4H, m), 4.10 (2H, m), 4.64 (1H, m), 5.56 (1H, br s, OH), 7.05-7.75 (8H, m), 7.75-8.10 (7H, m), 8.20 (1H, s)
(-)ESI-MS (m/z): 550 (free, $M-H)^-$

(22) Sodium 4'-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl)amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate
NMR (DMSO-d_6, δ): 2.60-3.05 (4H, m), 4.12 (2H, m), 4.66 (1H, m), 5.58 (1H, br s, OH), 7.15 (2H, d, J=8Hz), 7.17-7.50 (4H, m), 7.63 (2H, d, J=8Hz), 7.80-8.18 (8H, m)
(+)ESI-MS (m/z): 550 (free, $M+H)^+$

(23) Sodium 4'-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR (DMSO-d_6, δ): 1.67 (2H, quintet, J=7Hz), 2.40-2.80 (6H, m), 4.60 (1H, m), 5.48 (1H, br s, OH), 7.10-8.28 (16H, m)
(+)ESI-MS (m/z): 550 (free, $M+H)^+$

(24) Sodium 4'-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate
NMR (DMSO-d_6, δ): 1.67 (2H, quintet, J=7Hz), 2.40-2.80 (6H, m), 4.61 (1H, m), 5.53 (1H, br s, OH), 7.05-8.20 (16H, m)
(+)ESI-MS (m/z): 550 (free, $M+H)^+$

(25) Sodium 3-[4-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 1.67 (2H, quintet, J=7Hz), 2.40-2.80 (6H, m), 4.60 (1H, m), 5.51 (1H, br s, OH), 6.95-8.00 (16H, m)

(+)ESI-MS (m/z): 566 (free, $M+H)^+$

(26) Sodium 3'-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR (DMSO-d_6, δ): 1.65 (2H, quintet, J=7Hz), 2.40-2.80 (6H, m), 4.61 (1H, m), 5.68 (1H, br s, OH), 7.10-8.30 (1H, m)

(+)ESI-MS (m/z): 550 (free, $M+H)^+$

(27) Sodium 3-[3-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 1.65 (2H, quintet, J=7Hz), 2.40-2.80 (6H, m), 4.61 (1H, m), 6.90-8.05 (16H, m)

(+)ESI-MS (m/z): 566 (free, $M+H)^+$

(28) Sodium 5-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate

NMR (DMSO-d_6, δ): 1.64 (2H, quintet, J=7Hz), 2.40-2.90 (6H, m), 4.63 (1H, m), 6.73 (1H, d, J=9Hz), 7.10-7.50 (6H, m), 7.66 (1H, dd, J=9, 2Hz), 7.75 (2H, d, J=8Hz), 8.14 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 490 (free, $M+H)^+$

(29) Sodium 4-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-

hydroxybenzoate
NMR (DMSO-d_6, δ): 1.77 (2H, quintet, J=7Hz), 2.50-2.90 (6H, m), 4.72 (1H, m), 7.00-7.55 (8H, m), 7.83 (2H, d, J=8Hz), 7.84 (1H, d, J=8Hz)
(+)ESI-MS (m/z): 490 (free, $M+H)^+$

(30) Sodium 5-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-2-hydroxybenzoate
NMR (DMSO-d_6, δ): 2.55-3.05 (4H, m), 4.08 (2H, m), 4.64 (1H, m), 5.45 (1H, br s, OH), 6.72 (1H, d, J=9Hz), 7.09 (2H, d, J=9Hz), 7.15-7.45 (4H, m), 7.64 (1H, dd, J=9, 2Hz), 7.77 (2H, d, J=9Hz), 8.12 (1H, d, J=2Hz)
(-)ESI-MS (m/z): 490 (free, $M-H)^-$

(31) Sodium 5-[[4-[[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]-2-hydroxybenzoate
NMR (DMSO-d_6, δ): 1.21 (3H, d, J=6Hz), 2.75-3.55 (3H, m), 4.09 (2H, m), 4.80 (1H, m), 5.91 (1H, br s, OH), 6.70 (1H, d, J=9Hz), 7.11 (2H, d, J=9Hz), 7.22-7.50 (4H, m), 7.63 (1H, dd, J=9, 2Hz), 7.80 (2H, d, J=9Hz), 8.09 (1H, d, J=2Hz)
(-)ESI-MS (m/z): 504 (free, $M-H)^-$

(32) Sodium 2-chloro-4-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate
NMR (DMSO-d_6, δ): 1.69 (2H, quintet, J=7Hz), 2.32-2.82 (6H, m), 4.63 (1H, m), 5.55 (1H, br s, OH), 7.17-7.55 (7H, m), 7.60-7.86 (2H, m), 7.86 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 508 (free, $M+H)^+$

(33) Sodium 5-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-

hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methoxybenzoate

NMR (DMSO-d_6, δ): 1.66 (2H, quintet, J=7Hz), 2.32-2.75 (6H, m), 3.73 (3H, s), 4.56 (1H, m), 5.47 (1H, br s, OH), 7.02 (1H, d, J=9Hz), 7.15-7.48 (6H, m), 7.55 (1H, d, J=2Hz), 7.69 (1H, dd, J=9, 2Hz), 7.76 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 504 (free, $M+H)^+$

Example 6

Under nitrogen, a mixture of ethyl 4-[[4-[2-(benzylamino)ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (215 mg) and (R)-2-(3-chlorophenyl)oxirane (90.7 mg) in ethanol (10 ml) was refluxed for 48 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3:1 to 3:2) to give ethyl (R)-4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]-2-hydroxybenzoate (208 mg).

NMR ($CDCl_3$, δ): 1.40 (3H, t, J=7.1Hz), 2.55-2.9 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.96 (1H, d, J=13.4Hz), 4.42 (2H, q, J=7.1Hz), 4.6-4.65 (1H, m), 7.15-7.35 (11H, m), 7.4-7.45 (1H, m), 7.5 (1H, m), 7.82 (2H, d, J=8.4Hz), 7.95 (1H, d, J=8.3Hz)

(+)ESI-MS (m/z): 594, 596 $(M+H)^+$

Example 7

To a solution of ethyl (R)-4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (204 mg) in ethyl acetate (3 ml) was added 4N hydrogen chloride in ethyl acetate (0.5 ml) at room temperature, and the mixture was evaporated under reduced pressure. A mixture of the residue and 10% palladium on activated carbon (50% wet, 10 mg) in a mixture of ethanol (1.5 ml) and chlorobenzene (3.5 ml) was stirred at room

temperature in the presence of hydrogen at an atmospheric pressure for 2 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate which contained a little of methanol. After separation, the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20:1 to 15:1) to give ethyl (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (149 mg).

NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7.2Hz), 2.65-3.0 (6H, m), 4.43 (2H, q, J=7.2Hz), 4.6-4.65 (1H, m), 7.15-7.45 (7H, m), 7.52 (1H, m), 7.85-7.9 (2H, m), 7.97 (1H, d, J=8.4Hz)

(+)ESI-MS (m/z): 504, 506 $(M+H)^+$

Example 8

To a suspension of ethyl (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (145 mg) in methanol (3 ml) was added 1N sodiumhydroxide (0.72 ml) at room temperature, and the mixture was stirred at the same temperature for 4 days. To the resulting mixture was added 1N hydrochloric acid (0.43 ml), and the mixture was evaporated under reduced pressure. The residue was purified by reversed phase chromatography to give sodium (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2-hydroxybenzoate (110 mg).

NMR (DMSO-d_6, δ): 2.85-3.2 (6H, m), 4.75-4.9 (1H, m), 7.0-7.1 (2H, m), 7.25-7.55 (6H, m), 7.75-7.9 (3H, m)

(-)ESI-MS (m/z): 474, 476 $(M-Na)^-$

Example 9

The following compounds were obtained according to a similar manner to that of Example 7.

(1) Ethyl (R)-2-[4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.08 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m), 4.17 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.6, 8.7Hz), 6.85-7.0 (2H, m), 7.05-7.4 (8H, m), 7.5-7.6 (1H, m), 7.8-8.0 (5H, m)

(+)ESI-MS (m/z): 580, 582 $(M+H)^+$

(2) Ethyl (R)-2-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl)amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.07 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m), 4.15 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.6, 8.8Hz), 7.0-7.1 (2H, m), 7.15-7.65 (11H, m), 7.8-7.9 (2H, m), 7.95-8.0 (1H, m)

(+)ESI-MS (m/z): 580 $(M+H)^+$

(3) Ethyl (R)-[4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl]acetate

NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m), 3.65 (2H, s), 4.14 (2H, q, J=7.1Hz), 4.63 (1H, dd, J=3.7, 8.8Hz), 7.15-7.35 (6H, m), 7.42 (2H, d, J=8.3Hz), 7.8-7.95 (4H, m)

(+)ESI-MS (m/z): 502, 504 $(M+H)^+$

(4) Methyl (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR ($CDCl_3$, δ): 2.6-3.0 (6H, m), 3.95 (3H, s), 4.62 (1H, dd, J=3.6, 8.7Hz), 7.1-7.4 (6H, m), 7.55-7.7 (3H,

m), 7.75-8.0 (4H, m), 8.1-8.2 (3H, m)
(+)ESI-MS (m/z): 550, 552 $(M+H)^+$

(5) Ethyl (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.42 (3H, t, J=7.2Hz), 2.6-3.0 (6H, m), 4.42 (2H, q, J=7.2Hz), 4.63 (1H, dd, J=3.6, 8.7Hz), 7.1-7.4 (6H, m), 7.5-7.7 (2H, m), 7.7-8.0 (5H, m), 8.05-8.3 (3H, m)
(+)ESI-MS (m/z): 564, 566 $(M+H)^+$

(6) Ethyl (R)-3'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-2-carboxylate
NMR ($CDCl_3$, δ): 0.87 (3H, t, J=7.1Hz), 2.6-2.7 (1H, m), 2.8-3.0 (5H, m), 3.96 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.5, 8.9Hz), 7.15-7.35 (7H, m), 7.45-7.6 (4H, m), 7.85-8.0 (5H, m)
(+)ESI-MS (m/z): 564 $(M+H)^+$

(7) Ethyl (R)-4-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate
NMR ($CDCl_3$, δ): 1.40 (3H, t, J=7.1Hz), 2.6-3.05 (6H, m), 4.38 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.7, 8.8Hz), 6.95-7.05 (2H, m), 7.15-7.35 (7H, m), 7.4-7.75 (3H, m), 7.8-7.9 (2H, m), 8.0-8.1 (2H, m)
(-)ESI-MS (m/z): 578, 580 $(M-H)^-$

(8) Ethyl (R)-3-[3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate
NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m), 4.37 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.7, 8.8Hz),

7.1-7.7 (13H, m), 7.8-7.9 (3H, m)
(+)ESI-MS (m/z): 580, 582 $(M+H)^+$

(9) Ethyl (R)-4'-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-2'-hydroxy-1,1'-biphenyl-3-carboxylate
NMR ($CDCl_3$, δ): 1.37 (3H, t, J=7.1Hz), 2.6-3.0 (6H, m), 4.38 (2H, q, J=7.1Hz), 4.65 (1H, dd, J=3.6, 8.8Hz), 7.1-7.7 (10H, m), 7.90 (2H, d, J=8.3Hz), 8.0-8.1 (1H, m), 8.16 (1H, m)
(+)ESI-MS (m/z): 580, 582 $(M+H)^+$

(10) Ethyl [2-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate
NMR ($CDCl_3$, δ): 1.07 (3H, d, J=6Hz), 1.24 (3H, t, J=7Hz), 2.50-3.05 (5H, m), 4.18 (2H, q, J=7Hz), 4.52 (1H, dd, J=9, 4Hz), 4.59 (2H, s), 6.80 (1H, d, J=8Hz), 7.02-7.40 (7H, m), 7.52 (1H, t, J=8Hz), 7.99 (2H, d, J=8Hz), 8.20 (1H, d, J=8Hz)
(+)ESI-MS (m/z): 532 (free, $M+H)^+$

(11) Ethyl 2-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate
NMR ($CDCl_3$, δ): 1.06 (3H, d, J=6Hz), 1.38 (3H, t, J=7Hz), 2.50-3.05 (5H, m), 4.42 (2H, q, J=7Hz), 4.53 (1H, dd, J=9, 4Hz), 7.00-8.20 (12H, m)
(+)ESI-MS (m/z): 502 $(M+H)^+$

Example 10

Under nitrogen, a mixture of ethyl 4-[[4-(3-aminopropyl)phenyl]sulfonyl]-2-methylbenzoate (3.42 g) and (R)-2-(3-chlorophenyl)oxirane (731 mg) in ethanol (34 ml) was refluxed for 24 hours. The resulting mixture was evaporated under reduced pressure. The residue was purified

by column chromatography on silica gel (chloroform/methanol = 20:1 to 40:3) to give ethyl (R)-4-[[4-[3-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methylbenzoate (1.44 g).

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7.1Hz), 1.7-1.9 (2H, m), 2.55-2.9 (7H, m), 4.36 (2H, q, J=7.1Hz), 4.64 (1H, dd, J=3.6, 8.7Hz), 7.15-7.4 (6H, m), 7.7-8.0 (5H, m)

(+)ESI-MS (m/z): 516, 518 $(M+H)^+$

Example 11

To a suspension of ethyl (R)-4-[[4-[3-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methylbenzoate (1.42 g) in ethanol (14 ml) was added 1N sodiumhydroxide (2.75 ml) at room temperature, and the mixture was stirred at 60°C for 1.3 hours. The resulting mixture was evaporated under reduced pressure and dried in vacuo to give sodium (R)-4-[[4-[3-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-methylbenzoate (1.42g).

NMR (DMSO-d_6, δ): 1.55-1.75 (2H, m), 2.35-2.7 (9H, m), 4.55-4.65 (1H, m), 7.2-7.65 (9H, m), 7.81 (2H, d, J=8.2Hz)

(-)ESI-MS (m/z): 486, 488 $(M-Na)^-$

Example 12

The following compound was obtained according to a similar manner to that of Example 11.

Sodium (R)-[4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl]acetate

NMR (DMSO-d_6, δ): 2.55-2.8 (6H, m), 3.23 (2H, s), 4.55-4.65 (1H, m), 7.2-7.45 (8H, m), 7.7-7.85 (4H, m)

(+)ESI-MS (m/z): 472, 474 $(M-Na)^-$

Example 13

A mixture of (R)-4-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol (1.31 g), triethylamine (3.3 ml) and 10% palladium on activated carbon (50% wet, 0.65 g) in a mixture of methanol (13 ml) and chlorobenzene (13 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 5 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was dissolved into a mixture of ethyl acetate and saturated aqueous sodium hydrogencarbonate. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol = 20:1 to 8:1) to give (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol (789 mg).

NMR (DMSO-d_6, δ): 2.55-2.85 (6H, m), 4.55-4.6 (1H, m), 6.9-6.95 (2H, m), 7.2-7.8 (4H, m)

(+)ESI-MS (m/z): 432, 434 $(M+H)^+$

Example 14

Under nitrogen at room temperature, to a solution of (R)-4-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenyl]sulfonyl]phenol (1.0 g) in tetrahydrofuran (8 ml) was added di-tert-butyl dicarbonate (0.56 g) in tetrahydrofuran (2 ml), and the mixture was stirred at the same temperature for 12 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1 to 1:1) to give tert-butyl (R)-[2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(4-hydroxyphenyl)sulfonyl]phenyl]-ethyl]carbamate (1.1 g).

NMR ($CDCl_3$, δ): 1.2-1.5 (9H, m), 2.6-2.95 (2H, m), 3.15-3.6 (4H, m), 4.8-4.95 (1H, m), 6.8-6.95 (2H, m), 7.15-7.45 (6H, m), 7.7-7.9 (2H, m)

(+)ESI-MS (m/z): 554, 556 $(M+Na)^+$

Example 15

A mixture of (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol (202 mg) and 10% palladium on activated carbon (50% wet, 100 mg) in a mixture of methanol (2 ml) and chlorobenzene (2 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 2 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, the organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol = 20:1 to 8:1) followed by treatment with 4N hydrogen chloride in 1,4-dioxane and dryness to give (R)-3-[[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]phenol hydrochloride (90 mg).

NMR (DMSO-d_6, δ): 2.9-3.5 (6H, m), 4.85-5.0 (1H, m), 7.0-7.1 (1H, m), 7.2-7.6 (9H, m), 7.85-7.95 (2H, m)

(+)APCI-MS (m/z): 432, 434 $(M-HCl+H)^+$

Example 16

Under nitrogen, to a solution of (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]phenol (3.55 g) and 2,6-lutidine (1.09 ml) in dichloromethane (35 ml) was added trifluoromethanesulfonic anhydride (1.26 ml) in dryice-acetone bath, and the mixture was stirred at the same temperature for 1 hour. The resulting mixture was poured

into 1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1 to 2:1) to give (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]-phenyl]sulfonyl]phenyl trifluoromethanesulfonate (3.95 g).

NMR ($CDCl_3$, δ): 2.5-2.9 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.90 (1H, d, J=13.4Hz), 4.60 (1H, dd, J=3.7, 9.9Hz), 7.1-7.35 (11H, m), 7.4-7.7 (2H, m), 7.8-8.0 (4H, m)

(+)ESI-MS (m/z): 654 $(M+H)^+$

Example 17

To a solution of (R)-3-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-phenyl trifluoromethanesulfonate (480 mg) and 2-carboxyphenylboronic acid (480 mg) in 1,2-dimethoxyethane (7 ml) were added tetrakis(triphenylphosphine)palladium(0) (42.4 mg) and 2M sodium carbonate (1.14 ml) at room temperature, and the mixture was stirred at 80°C for 10 hours. The resulting mixture was poured into pH 4 phosphate buffer and the aqueous mixture was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 30:1 to 20:1) to give (R)-3'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-2-carboxylic acid (354 mg).

NMR (DMSO-d_6, δ): 2.55-2.8 (6H, m), 3.58 (1H, d, J=13.9Hz), 3.73 (1H, d, J=13.9Hz), 4.6-4.75 (1H, m), 6.95-8.0 (21H, m)

(-)ESI-MS (m/z): 624 $(M-H)^-$

Example 18

To a solution of methyl 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate (125 mg) in 1,4-dioxane (1.3 ml) was added 1N sodium hydroxide solution (0.48 ml), and the mixture was stirred at 50°C for 19 hours. After the solution was made acidic with 1N hydrochloric acid, the mixture was extracted with chloroform-methanol. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylic acid (104 mg) as a white amorphous.

NMR (DMSO-d_6, δ): 1.07, 1.19 (total 9H, a pair of s), 2.70-2.95 (2H, m), 2.95-3.45 (4H, m), 4.71 (1H, m), 5.58 (1H, br s, OH), 7.10-7.53 (6H, m), 7.64 (1H, t, J=8Hz), 7.82-8.12 (8H, s), 8.20 (1H, s)

(-)ESI-MS (m/z): 634 $(M-H)^-$

Example 19

4'[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylic acid (91 mg) and 4N hydrogen chloride in 1,4-dioxane (0.92 ml) were mixed and stirred at room temperature for 15.5 hours. The solvent was evaporated and the residual powder was treated with ethanol (0.92 ml) - 1N sodium hydroxide solution (0.35 ml). The solvent was evaporated to give sodium 4'-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate (54 mg) as a white powder.

NMR (DMSO-d_6, δ): 2.50-2.90 (6H, m), 4.60 (1H, m), 5.48 (1H, br s, OH), 7.10-7.55 (7H, m), 7.55-7.72 (1H, m), 7.72-8.10 (7H, m), 8.20 (1H, s)

(-)ESI-MS (m/z): 534 (free, $M-H)^-$

Example 20

Ethyl 3-[4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-phenoxy]benzoate (48 mg) and 4N hydrogen chloride in 1,4-dioxane (1 ml) were mixed and stirred at room temperature for 6.5 hours. The solvent was evaporated and the residual powder was treated with ethanol (1 ml) - 1N sodium hydroxide solution (0.16 ml). After the mixture was heated to reflux for 9 hours, the solvent was evaporated to give sodium 3-[4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenyl]sulfonyl]phenoxy]benzoate (46 mg) as a white powder.

NMR (DMSO-d_6, δ): 2.50-2.90 (6H, m),4.60 (1H, m), 5.50 (1H, br s, OH), 6.95-7.16 (3H, m), 7.16-7.60 (8H, m), 7.65-8.00 (5H, m)

(+)ESI-MS (m/z): 552 (free, $M+H)^+$

Example 21

Under nitrogen atmosphere, a mixture of 4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate (265 mg), palladium(II) acetate (5 mg), 2-[bis(tert-butyl)phosphino]biphenyl (12 mg), and powdered potassium phosphate (177 mg) in toluene (2.6 ml) was heated to 100°C for 10 hours. After being allowed to cool to room temperature, the mixture was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give ethyl 4-[4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenyl]sulfonyl]phenoxy]benzoate (93 mg) as a white amorphous.

NMR ($CDCl_3$, δ): 1.36 (9H, br s), 1.40 (3H, t, J=7Hz), 2.60-3.05 (2H, m), 3.05-3.60 (4H, m), 4.27 (1H, br

s, OH), 4.38 (2H, q, J=7Hz), 4.86 (1H, m), 6.90-7.45 (10H, m), 7.86 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 8.07 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 702 $(M+Na)^+$

Example 22

To a solution of 3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenol (282 mg) in N,N-dimethylformamide (2.3 ml) were added powdered potassium carbonate (88 mg) and ethyl bromoacetate (0.07 ml), and the mixture was stirred at 60°C for 1.5 hours. After being allowed to cool to room temperature, the mixture was partitioned between hexane/ethyl acetate (1/2) and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give ethyl [3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]acetate (270 mg) as a colorless oil.

NMR ($CDCl_3$, δ): 1.29 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.35-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 4.26 (2H, q, J=7Hz), 4.61 (1H, dd, J=10, 4Hz), 4.65 (2H, s), 7.00-7.62 (15H, m), 7.80 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 622 $(M+H)^+$

Example 23

To a solution of ethyl [3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]acetate (252 mg) in ethyl acetate (2.5 ml) was added 4N hydrogen chloride/ethyl acetate (0.5 ml). After the solvent was evaporated, the residue was dissolved in chlorobenzene (3.5 ml) - ethanol (1.5 ml), and the solution was hydrogenated (1 atm) over 10% palladium on carbon (12

mg) at room temperature for 3.5 hours. After the catalyst was filtered off, the filtrate was concentrated to give ethyl [3-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]phenyl]sulfonyl]phenoxy]acetate hydrochloride (221 mg) as a white powder.

NMR (DMSO-d_6, δ): 1.19 (3H, t, J=7Hz), 1.96 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.80-3.25 (4H, m), 4.15 (2H, q, J=7Hz), 4.92 (2H, s), 4.95 (1H, m), 6.29 (1H, br s, OH), 7.15-7.62 (10H, m), 7.92 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 532 (free, $M+H)^+$

Example 24

To a solution of 3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenol (287 mg) in dimethyl sulfoxide (1.5 ml) were added powdered potassium carbonate (115 mg) and 2-fluorobenzaldehyde (79 mg), and the mixture was stirred at 100°C for 4 hours. After being allowed to cool to room temperature, the mixture was partitioned between hexane/ethyl acetate (1/2) and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give 2-[3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]phenyl]sulfonyl]phenoxy]benzaldehyde (166 mg) as a colorless oil.

NMR ($CDCl_3$, δ): 1.81 (2H, quintet, J=7Hz), 2.35-2.80 (6H, m), 3.49 (1H, d, J=13Hz), 3.88 (1H, d, J=13Hz), 4.61 (1H, dd, J=10, 4Hz), 6.80-8.10 (21H, m), 10.40 (1H, s)

(+)ESI-MS (m/z): 640 $(M+H)^+$

Example 25

2-[3-[[4-[3-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]benzoic acid (171 mg) and 4N hydrogen chloride in 1,4-dioxane (1.7 ml) were mixed and stirred at room temperature for 15 hours. The solvent was evaporated to give [[4-[[4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoyl](methyl)-amino]acetic acid hydrochloride (163 mg) as a white amorphous.

NMR (DMSO-d_6, δ): 1.82-2.12 (2H, m), 2.74 (2H, t, J=7Hz), 2.83-3.30 (4H, m), 4.96 (1H, m), 6.31 (1H, br s, OH), 7.08-7.98 (16H, m)

(-)ESI-MS (m/z): 564 (free, $M-H)^-$

Example 26

To a suspension of 3-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenol hydrochloride (324 mg) in tetrahydrofuran (3.2 ml) were added 1N sodium hydroxide solution (0.7 ml) and di-tert-butyl dicarbonate (169 mg), and the mixture was stirred at room temperature for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give tert-butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[(3-hydroxyphenyl)sulfonyl]phenyl]ethyl]carbamate (318 mg) as a white amorphous.

NMR ($CDCl_3$, δ): 1.33 (9H, s), 2.45-3.00 (2H, m) 3.00-3.65 (4H, m), 4.55 (1H, br s, OH), 4.71 (1H, m), 6.50-8.00 (12H, m)

(+)ESI-MS (m/z): 554 $(M+Na)^+$

Example 27

The following compounds were obtained according to a similar manner to that of Example 16.

(1) 4-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]phenyl trifluoromethanesulfonate
NMR (DMSO-d_6, δ): 1.31 (9H, br s), 2.60-3.05 (2H, m), 3.05-3.60 (4H, m), 4.24 (1H, br s, OH), 4.87 (1H, m), 7.05-7.48 (8H, m), 7.87 (2H, d, J=8Hz), 8.03 (2H, d, J=9Hz)
(+)APCI-MS (m/z): 564 $(M-Boc+H)^+$

(2) 3-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate
NMR ($CDCl_3$, δ): 1.87 (2H, quintet, J=7Hz), 2.43-2.90 (6H, m), 3.62 (1H, d, J=13Hz), 3.92 (1H, d, J=13H), 4.66 (1H, dd, J=10, 4Hz), 7.05-8.00 (17H, m)
(+)ESI-MS (m/z): 668 $(M+H)^+$

(3) 4-[[4-[2-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenyl trifluoromethanesulfonate
NMR ($CDCl_3$, δ): 2.65 (1H, dd, J=13, 10Hz), 2.84-3.22 (2H, m), 2.86 (1H, dd, J=13, 4Hz), 3.69 (1H, d, J=13Hz), 3.95 (1H, d, J=13Hz), 3.97-4.09 (2H, m), 4.65 (1H, dd, J=10, 4Hz), 6.95 (2H, d, J=8Hz), 7.10-7.38 (9H, m), 7.39 (2H, d, J=8Hz), 7.87 (2H, d, J=8Hz), 8.02 (2H, d, J=8Hz)
(+)ESI-MS (m/z): 670 $(M+H)^+$

(4) 2-[[4-[(2R)-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate
NMR ($CDCl_3$, δ): 1.03 (3H, d, J=6Hz), 2.35-2.95 (4H, m),

3.00-3.26 (1H, m), 3.51 (1H, d, J=13Hz), 3.84 (1H, d, J=13Hz), 4.53 (1H, dd, J=10, 4Hz), 6.85-7.95 (16H, m), 8.29 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 668 $(M+H)^+$

(5) 4-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenyl trifluoromethanesulfonate

NMR ($CDCl_3$, δ): 1.81 (2H, quintet, J=7Hz), 2.38-2.80 (6H, m), 3.49 (1H, d, J=13Hz), 3.88 (1H, d, J=13Hz), 4.61 (1H, dd, J=10, 4Hz), 7.05-7.50 (13H, m), 7.82 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 668 $(M+H)^+$

Example 28

The following compound was obtained according to a similar manner to that of Example 11.

Sodium 4-[[4-[[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]oxy]phenyl]sulfonyl]benzoate

NMR (DMSO-d_6, δ): 1.0-1.1 (3H, m), 2.65-2.75 (2H, m), 2.9-3.05 (1H, m), 3.75-3.9 (2H, m), 4.55-4.65 (1H, m), 7.05-7.15 (2H, m), 7.2-7.4 (4H, m), 7.75-7.9 (4H, m), 7.95-8.0 (2H, m)

(-)ESI-MS (m/z): 488 $(M-Na)^-$

Example 29

The following compound was obtained according to a similar manner to that of Example 18.

4'-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylic acid

NMR (DMSO-d_6, δ): 1.07, 1.19 (total 9H, a pair of s), 2.70-2.95 (2H, m), 2.95-3.45 (4H, m), 4.72 (1H, m),

5.59 (1H, br s, OH), 7.10-7.52 (6H, m), 7.75-8.12 (10H, m)

(-)ESI-MS (m/z): 634 $(M-H)^-$

Example 30

The following compound was obtained according to a similar manner to that of Example 19.

Sodium 4'-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR (DMSO-d_6, δ): 2.50-2.90 (6H, m), 4.60 (1H, m), 5.49 (1H, br s, OH), 7.10-7.72 (8H, m), 7.72-8.10 (8H, m)

(-)ESI-MS (m/z): 534 (free, $M-H)^-$

Example 31

The following compounds were obtained according to a similar manner to that of Example 20.

(1) Sodium 3-[4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 2.50-2.90 (6H, m), 4.63 (1H, m), 7.00-7.20 (3H, m), 7.20-7.55 (8H, m), 7.65-8.00 (5H, m)

(-)ESI-MS (m/z): 550 (free, $M-H)^-$

(2) Sodium 4-[4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR (DMSO-d_6, δ): 2.50-2.90 (6H, m), 4.61 (1H, m), 6.31 (1H, br s, OH), 6.90-8.10 (16H, m)

(-)ESI-MS (m/z): 550 (free, $M-H)^-$

(3) Sodium 2-[3-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-nicotinate

NMR (DMSO-d_6, δ): 1.67 (2H, quintet, J=7Hz), 2.30-2.80 (6H, m), 4.61 (1H, m), 5.54 (1H, br s, OH), 7.00-8.10 (15H, m)

(+)ESI-MS (m/z): 567 (free, $M+H)^+$

Example 32

The following compounds were obtained according to a similar manner to that of Example 21.

(1) Methyl 3-[4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.36 (9H, br s), 2.60-3.05 (2H, m), 3.05-3.60 (4H, m), 3.91 (3H, s), 4.31 (1H, br s, OH), 4.86 (1H, m), 7.00 (2H, d, J=9Hz), 7.10-7.40 (7H, m), 7.48 (1H, t, J=8Hz), 7.67 (1H, s), 7.75-7.98 (5H, m)

(+)ESI-MS (m/z): 688 $(M+Na)^+$

(2) Ethyl 3-[4-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate

NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7Hz), 1.81 (2H, quintet, J=7Hz), 2.37-2.80 (6H, m), 3.49 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 4.37 (2H, q, J=7Hz), 4.61 (1H, dd, J=10, 4Hz), 7.01 (2H, d, J=8Hz), 7.05-7.70 (15H, m), 7.81 (2H, d, J=8Hz), 7.89 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 684 $(M+H)^+$

Example 33

The following compounds were obtained according to a

similar manner to that of Example 22.

(1) Ethyl [2-[[4-[(2R)-2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-acetate

NMR ($CDCl_3$, δ): 1.02 (3H, d, J=6Hz), 1.24 (3H, t, J=7Hz), 2.40-2.90 (4H, m), 2.98-3.22 (1H, m), 3.48 (1H, d, J=13Hz), 3.82 (1H, d, J=13Hz), 4.19 (2H, q, J=7Hz), 4.52 (1H, dd, J=10, 4Hz), 4.59 (2H, s), 6.81 (1H, d, J=8Hz), 6.92-7.40 (12H, m), 7.51 (1H, t, J=8Hz), 7.94 (2H, d, J=8Hz), 8.17 (1H, d, J=8Hz)

(+)ESI-MS (m/z): 644 $(M+Na)^+$

(2) Ethyl [4-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenoxy]-acetate

NMR ($CDCl_3$, δ): 1.29 (3H, t, J=7Hz) 2.64 (1H, dd, J=13, 10Hz), 2.80-3.22 (2H, m), 2.85 (1H, dd, J=13, 4Hz), 3.69 (1H, d, J=13Hz), 3.94-4.10 (2H, m), 4.01 (1H, d, J=13Hz), 4.26 (2H, q, J=7Hz), 4.64 (1H, dd, J=10, 3Hz), 4.65 (2H, s), 6.91 (2H, d, J=8Hz), 6.95 (2H, d, J=8Hz), 7.06-7.40 (9H, m), 7.83 (2H, d, J=8Hz), 7.86 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 624 $(M+H)^+$

Example 34

The following compounds were obtained according to a similar manner to that of Example 23.

(1) Ethyl 4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]benzoate hydrochloride

NMR (DMSO-d_6, δ): 1.32 (3H, t, J=7Hz), 2.95-3.55 (4H, m), 4.34 (2H, q, J=7Hz), 4.40 (2H, m), 5.02 (1H,

m), 6.32 (1H, br s, OH), 7.20 (2H, d, J=8Hz), 7.30-7.50 (4H, m), 7.95 (2H, d, J=8Hz), 8.06 (2H, d, J=8Hz), 8.14 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 534 (free, $M+H)^+$

(2) Ethyl [4-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]phenoxy]-acetate hydrochloride

NMR (DMSO-d_6, δ): 1.20 (3H, t, J=7Hz), 2.95-3.50 (4H, m), 4.16 (2H, q, J=7Hz), 4.39 (2H, m), 4.90 (2H, s), 5.01 (1H, m), 6.32 (1H, br s, OH), 7.11 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 7.30-7.50 (4H, m), 7.84 (2H, d, J=8Hz), 7.89 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 534 (free, $M+H)^+$

(3) Ethyl 3-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate hydrochloride

NMR (DMSO-d_6, δ): 1.34 (3H, t, J=7Hz), 1.96 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.80–3.25 (4H, m), 4.36 (2H, q, J=7Hz), 4.96 (1H, m), 6.30 (1H, br s, OH), 7.26-7.60 (6H, m), 7.80 (1H, t, J=8Hz), 7.95 (2H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.39 (1H, s)

(+)ESI-MS (m/z): 502 (free, $M+H)^+$

(4) Ethyl 4'-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate hydrochloride

NMR (DMSO-d_6, δ): 1.34 (3H, t, J=7Hz), 2.95-3.55 (4H, m), 4.35 (2H, q, J=7Hz), 4.40 (2H, m), 5.00 (1H, m), 6.33 (1H, br s, OH), 7.20 (2H, d, J=8Hz), 7.30-7.53 (5H, m), 7.67 (1H, t, J=8Hz), 7.85-8.13 (7H, m), 8.20 (1H, s)

(+)ESI-MS (m/z): 580 (free, $M+H)^+$

(5) Methyl 4'-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate hydrochloride

NMR (DMSO-d_6, δ): 2.98-3.50 (4H, m), 3.88 (3H, s), 4.40 (2H, m), 5.01 (1H, m), 6.32 (1H, br s, OH), 7.20 (2H, d, J=8Hz), 7.28-7.50 (4H, m), 7.80-8.15 (10H, m)

(+)ESI-MS (m/z): 566 (free, $M+H)^+$

(6) Ethyl 4'-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate hydrochloride

NMR (DMSO-d_6, δ): 1.34 (3H, t, J=7Hz), 1.97 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.82-3.25 (4H, m), 4.35 (2H, q, J=7Hz), 4.95 (1H, m), 6.29 (1H, br s, OH), 7.20-8.28 (16H, m)

(+)ESI-MS (m/z): 578 (free, $M+H)^+$

(7) Methyl 4'-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate hydrochloride

NMR (DMSO-d_6, δ): 1.97 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.82-3.22 (4H, m), 3.88 (3H, s), 4.97 (1H, m), 6.29 (1H, br s, OH) 7.20-7.60 (6H, m), 7.80-8.15 (10H, m)

(+)ESI-MS (m/z): 564 (free, $M+H)^+$

(8) Ethyl 3-[4-[[4-[3-[[(2R)-2-(3-chlorophenyl)-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate hydrochloride

NMR (DMSO-d_6, δ): 1.30 (3H, t, J=7Hz), 1.96 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.80-3.30 (4H, m), 4.28 (2H, q, J=7Hz), 4.94 (1H, m), 6.30 (1H, br s, OH), 7.16 (2H, d, J=8Hz), 7.22-8.05

(14H, m)
(+)ESI-MS (m/z): 594 (free, $M+H)^+$

(9) Ethyl 3'-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate hydrochloride
NMR (DMSO-d_6, δ): 1.35 (3H, t, J=7Hz), 1.97 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.79-3.30 (4H, m), 4.37 (2H, q, J=7Hz), 4.95 (1H, m), 6.30 (1H, br s, OH), 7.25-8.30 (16H, m)
(+)ESI-MS (m/z): 578 (free, $M+H)^+$

(10) Ethyl 3-[3-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate hydrochloride
NMR (DMSO-d_6, δ): 1.30 (3H, t, J=7Hz), 1.97 (2H, quintet, J=7Hz), 2.74 (2H, t, J=7Hz), 2.80-3.30 (4H, m), 4.31 (2H, q, J=7Hz), 4.95 (1H, m), 6.30 (1H, br s, OH), 7.20-8.00 (16H, m)
(+)ESI-MS (m/z): 594 (free, $M+H)^+$

(11) Sodium 2-[3-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]-benzoate
NMR (DMSO-d_6, δ): 1.66 (2H, quintet, J=7Hz), 2.35-2.80 (6H, m), 4.60 (1H, m), 5.54 (1H, br s, OH), 6.80-7.95 (16H, m)
(-)ESI-MS (m/z): 564 (free, $M-H)^-$

(12) 3-[[4-[3-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenol hydrochloride
NMR (DMSO-d_6, δ): 1.97 (2H, quintet, J=7Hz), 2.73 (2H, t, J=7Hz), 2.75-3.30 (4H, m), 4.96 (1H, m), 6.30 (1H, br s, OH), 6.95-7.60 (10H, m), 7.86 (2H, d,

J=8Hz), 8.75 (1H, br s), 9.03 (1H, br s), 10.32 (1H, s, OH)

(+)ESI-MS (m/z): 446 (free, $M+H)^+$

(13) Ethyl 5-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride

NMR (DMSO-d_6, δ): 1.34 (3H, t, J=7Hz), 2.00 (2H, quintet, J=7Hz), 2.60-3.25 (6H, m), 4.37 (2H, q, J=7Hz), 4.96 (1H, m), 6.28 (1H, br s, OH) 7.19 (1H, d, J=9Hz), 7.25-7.60 (6H, m), 7.88 (2H, d, J=8Hz), 8.00 (1H, dd, J=9, 2Hz), 8.23 (1H, d, J=2Hz)

(+)ESI-MS (m/z): 518 (free, $M+H)^+$

(14) Ethyl 4-[[4-[3-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride

NMR (DMSO-d_6, δ): 1.30 (3H, t, J=7Hz), 1.97 (2H, quintet, J=7Hz), 2.60-3.30 (6H, m), 4.33 (2H, q, J=7Hz), 4.96 (1H, m), 6.29 (1H, br s, OH), 7.20-7.62 (8H, m), 7.77-8.03 (3H, m)

(+)ESI-MS (m/z): 518 (free, $M+H)^+$

(15) Ethyl 5-[[4-[2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-2-hydroxybenzoate hydrochloride

NMR (DMSO-d_6, δ): 1.34 (3H, t, J=7Hz), 2.95-3.55 (4H, m), 4.37 (2H, q, J=7Hz), 4.38 (2H, m), 5.01 (1H, m), 6.33 (1H, br s, OH), 7.18 (2H, d, J=9Hz), 7.25-7.55 (5H, m), 7.91 (2H, d, J=9Hz), 7.98 (1H, dd, J=9, 2Hz), 8.21 (12H, d, J=2Hz), 11.27 (1H, br s, OH)

(+)ESI-MS (m/z): 520 (free, $M+H)^+$

Example 35

The following compounds were obtained according to a similar manner to that of Example 24.

(1) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][3-[4-[[3-(2-formylphenoxy)phenyl]sulfonyl]phenyl]propyl]-carbamate
NMR ($CDCl_3$, δ): 1.44 (9H, s), 1.60-1.95 (2H, m), 2.61 (2H, t, J=7Hz), 2.90-3.60 (4H, m), 4.47 (1H, br s, OH), 4.89 (1H, m), 6.91 (1H, d, J=8Hz), 7.10-8.02 (15H, m), 10.39 (1H, s)
(+)ESI-MS (m/z): 672 $(M+Na)^+$

(2) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[[3-[(3-formyl-2-pyridyl)oxy]phenyl]sulfonyl]-phenyl]ethyl]carbamate
NMR ($CDCl_3$, δ): 1.36 (9H, s), 2.60-3.02 (2H, m), 3.02-3.60 (4H, m), 4.29 (1H, br s, OH), 4.87 (1H, m), 7.05-7.65 (9H, m), 7.70-8.00 (4H, m), 8.20-8.40 (2H, m)
(-)ESI-MS (m/z): 635 $(M-H)^-$

(3) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][2-[4-[[4-[(3-formyl-2-pyridyl)oxy]phenyl]sulfonyl]-phenyl]ethyl]carbamate
NMR ($CDCl_3$, δ): 1.36 (9H, s), 2.60-3.00 (2H, m), 3.05-3.60 (4H, m), 4.30 (1H, br s, OH), 4.88 (1H, m), 7.10-7.45 (9H, m), 7.89 (2H, d, J=8Hz), 8.00 (2H, d, J=8Hz), 8.20-8.40 (2H, m)
(-)ESI-MS (m/z): 635 $(M-H)^-$

(4) tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][3-[4-[[3-[(3-formyl-2-pyridyl)oxy]phenyl]sulfonyl]-phenyl]propyl]carbamade
NMR ($CDCl_3$, δ): 1.44 (9H, s), 1.76 (2H, quintet, J=7Hz), 2.61 (2H, m), 2.85-3.55 (4H, m), 4.48 (1H, br s,

OH), 4.88 (1H, m), 7.05-7.65 (9H, m), 7.70-8.00 (4H, m), 8.20-8.36 (2H, m), 10.51 (1H, s)

(-)ESI-MS (m/z): 649 $(M-H)^-$

Example 36

The following compounds were obtained according to a similar manner to that of Example 25.

(1) 2-[3-[[4-[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-nicotinic acid dihydrochloride

NMR (DMSO-d_6, δ): 2.90-3.40 (6H, m), 4.99 (1H, m) 6.34 (1H, br s, OH), 7.20-7.90 (11H, m), 7.97 (2H, d, J=8Hz), 8.20-8.40 (2H, m)

(+)ESI-MS (m/z): 553 (free, $M+H)^+$

(2) 2-[4-[[4-[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]phenoxy]-nicotinic acid dihydrochloride

NMR (DMSO-d_6, δ): 2.90-3.40 (6H, m), 4.99 (1H, m), 6.34 (1H, br s, OH), 7.22-7.62 (9H, m), 7.96 (2H, d, J=8Hz), 7.99 (2H, d, J=8Hz), 8.23-8.40 (2H, m)

(-)ESI-MS (m/z): 551 (free, $M-H)^-$

Example 37

The following compound was obtained according to a similar manner to that of Example 26.

tert-Butyl [(2R)-2-(3-chlorophenyl)-2-hydroxyethyl][3-[4-[(3-hydroxyphenyl)sulfonyl]phenyl]propyl]carbamate

NMR ($CDCl_3$, δ): 1.43 (9H, s), 1.78 (2H, quintet, J=7Hz), 2.60 (2H, t, J=7Hz), 2.85-3.50 (4H, m), 4.58 (1H, br s, OH), 4.86 (1H, m), 6.84 (1H, br s, OH), 6.92-7.52 (10H, m), 7.81 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 568 $(M+Na)^+$

Example 38

The following compound was obtained according to a similar manner to that of Preparation 24 starting from the object compound of Example 14.

Ethyl 3-[4-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.37 (9H, br s), 1.38 (3H, t, J=7Hz), 2.60-3.05 (2H, m), 3.05-3.60 (4H, d), 4.33 (1H, br s, OH), 4.37 (2H, q, J=7Hz), 4.87 (1H, m), 7.00 (2H, d, J=9Hz), 7.10-7.42 (7H, m), 7.47 (1H, t, J=8Hz), 7.69 (1H, s), 7.74-7.96 (5H, m)

(+)ESI-MS (m/z): 702 $(M+Na)^+$

Example 39

The following compound was obtained according to a similar manner to that of Preparation 24 starting from the object compound of Example 3-(16).

Ethyl 3-[3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]benzoate

NMR ($CDCl_3$, δ): 1.38 (3H, t, J=7Hz), 1.81 (2H, quintet, J=7Hz), 2.35-2.83 (6H, m), 3.49 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 3.91 (1H, br s, OH), 4.37 (2H, q, J=7Hz), 4.61 (1H, dd, J=10 and 4Hz), 7.05-7.95 (21H, m)

(+)ESI-MS (m/z): 684 $(M+H)^+$

Example 40

The following compounds were obtained according to a similar manner to that of Preparation 60 starting from the object compound of Example 16.

(1) Methyl (R)-3'-[[4-[2-[benyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR ($CDCl_3$, δ): 2.5-2.9 (6H, m), 3.53 (1H, d, J=13.4Hz), 3.90 (1H, d, J=13.4Hz), 3.95 (3H, s), 4.59 (1H, dd, J=3.7, 9.8Hz), 7.1-7.35 (11H, m), 7.55-7.7 (3H, m), 7.75-8.0 (4H, m), 8.1-8.2 (3H, m)

(+)ESI-MS (m/z): 640, 642 $(M+H)^+$

(2) Ethyl (R)-3'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.42 (3H, t, J=7.2Hz), 2.5-2.9 (6H, m), 3.54 (1H, d, J=13.4Hz), 3.89 (1H, d, J=13.4Hz), 4.42 (2H, q, J=7.2Hz), 4.60 (1H, dd, J=3.6, 9.9Hz), 7.1-7.35 (11H, m), 7.45-7.65 (2H, m), 7.75-8.0 (5H, m), 8.05-8.3 (3H, m)

(+)ESI-MS (m/z): 654, 656 $(M+H)^+$

Example 41

The following compounds were obtained according to a similar manner to that of Preparation 60 starting from the object compound of Example 27-(1).

(1) Methyl 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.34 (9H, br s) 2.60-3.00 (2H, m), 3.00-3.70 (4H, m), 3.95 (3H, s), 4.30 (1H, br s, OH), 4.85 (1H, m), 7.10-7.42 (6H, m), 7.55 (1H, t, J=8Hz), 7.63-7.82 (3H, m), 7.90 (2H, d, J=8Hz), 8.00 (2H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.23 (1H, s)

(+)ESI-MS (m/z): 672$(M+Na)^+$

(2) Methyl 4'-[[4-[2-[(tert-butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]-sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR ($CDCl_3$, δ): 1.34 (9H, br s),2.60-3.04 (2H, m), 3.04-3.70 (4H, m), 3.95 (3H, s), 4.28 (1H, br s, OH), 4.84 (1H, m), 7.08-7.42 (6H, m), 7.61 (2H, d, J=8Hz), 7.70 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 8.01 (2H, d, J=8Hz), 8.12 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 672 $(M+Na)^+$

Example 42

The following compounds were obtained according to a similar manner to that of Preparation 60 starting from the object compound of Example 27-(3).

(1) Ethyl 4'-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7Hz), 2.64 (1H, dd, J=13, 10Hz), 2.85 (1H, dd, J=13, 4Hz), 2.86-3.20 (2H, m), 3.69 (1H, d, J=13Hz), 3.94 (1H, d, J=13Hz), 3.96 (br s, OH), 3.96-4.10 (2H, m), 4.41 (2H, q, J=7Hz), 4.64 (1H, dd, J=10, 3Hz), 6.94 (2H, d, J=8Hz), 7.08-7.40 (9H, m), 7.53 (1H, t, J=8Hz), 7.63-7.82 (3H, m), 7.90 (2H, d, J=8Hz), 8.00 (2H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.23 (1H, s)

(+)ESI-MS (m/z): 670 $(M+H)^+$

(2) Methyl 4'-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]-1,1'-biphenyl-4-carboxylate

NMR ($CDCl_3$, δ): 2.64 (1H, dd, J=13, 10Hz), 2.85 (1H, dd, J=13, 4Hz), 2.86-3.20 (2H, m), 3.68 (1H, d, J=13Hz), 3.94 (3H, s), 3.94 (1H, d, J=13Hz), 3.96-4.10 (2H, m), 4.64 (1H, dd, J=10, 3Hz), 6.94 (2H,

d, J=8Hz), 7.08-7.42 (9H, m), 7.63 (2H, d, J=8Hz), 7.72 2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 8.00 (2H, d, J=8Hz), 8.12 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 656 $(M+H)^+$

Example 43

The following compounds were obtained according to a similar manner to that of Preparation 60 starting from the object compound of Example 27-(5).

(1) Ethyl 4'-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7Hz), 1.81 (2H, quintet, J=7Hz), 2.32-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 3.90 (1H, br s, OH), 4.41 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.05-7.40 (11H, m), 7.53 (1H, t, J=8Hz), 7.62-7.84 (3H, m), 7.86 (2H, d, J=8Hz), 8.02 (2H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.23 (1H, s)

(+)ESI-MS (m/z): 668 $(M+H)^+$

(2) Methyl 4'-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1-biphenyl-4-carboxylate

NMR ($CDCl_3$, δ): 1.81 (2H, quintet, J=7Hz), 2.35-2.80 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 3.95 (3H, s), 4.60 (1H, dd, J=10, 4Hz), 7.05-7.40 (11H, m), 7.62 (2H, d, J=8Hz), 7.72 (2H, d, J=8Hz), 7.86 (2H, d, J=8Hz), 8.02 (2H, d, J=8Hz), 8.12 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 654 $(M+Na)^+$

Example 44

The following compound was obtained according to a

similar manner to that of Preparation 60 starting from the object compound of Example 27-(2).

Ethyl 3'-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-1,1'-biphenyl-3-carboxylate

NMR ($CDCl_3$, δ): 1.42 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.32-2.78 (6H, m), 3.48 (1H, d, J=13Hz), 3.86 (1H, d, J=13Hz), 4.43 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.03-8.30 (21H, m)

(+)ESI-MS (m/z): 668 $(M+H)^+$

Example 45

The following compound was obtained according to a similar manner to that of Preparation 11 starting from the object compound of Example 27-(3).

Ethyl 4-[[4-[2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethoxy]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.39 (3H, t, J=7Hz), 2.64 (1H, dd, J=13, 10Hz), 2.84-3.22 (2H, m), 2.85 (1H, dd, J=13, 4Hz), 3.68 (1H, d, J=13Hz), 3.94 (1H, d, J=13Hz), 3.94-4.10 (2H, m), 4.39 (2H, q, J=7Hz), 4.64 (1H, dd, J=10, 3Hz), 6.93 (2H, d, J=8Hz), 7.05-7.40 (9H, m), 7.87 (2H, d, J=8Hz), 7.97 (2H, d, J=8Hz), 8.14 (2H, d, J=8Hz)

(+)ESI-MS (m/z): 594 $(M+H)^+$

Example 46

The following compound was obtained according to a similar manner to that of Preparation 11 starting from the object compound of Example 27-(2).

Ethyl 3-[[4-[3-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.41 (3H, t, J=7Hz), 1.80 (2H, quintet, J=7Hz), 2.32-2.75 (6H, m), 3.48 (1H, d, J=13Hz), 3.87 (1H, d, J=13Hz), 4.41 (2H, q, J=7Hz), 4.60 (1H, dd, J=10, 4Hz), 7.03-7.40 (11H, m), 7.59 (1H, t, J=8Hz), 7.84 (2H, d, J=8Hz), 8.11 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.59 (1H, s)

(+)ESI-MS (m/z): 592 $(M+H)^+$

Example 47

The following compound was obtained according to a similar manner to that of Preparation 11 starting from the object compound of Example 27-(4).

Ethyl 2-[[4-[(2R)-2-[benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]benzoate

NMR ($CDCl_3$, δ): 1.01 (3H, d, J=6Hz), 1.38 (3H, t, J=7Hz), 2.40-2.90 (4H, m), 2.98-3.22 (1H, m), 3.49 (1H, d, J=13Hz), 3.57 (1H, br s, OH), 3.83 (1H, d, J=13Hz), 4.43 (2H, q, J=7Hz), 4.58 (1H, dd, J=10, 4Hz), 6.85-8.20 (17H, m)

(+)ESI-MS (m/z): 592 $(M+H)^+$

Example 48

The following compound was obtained according to a similar manner to that of Preparation 33 starting from the object compound of Example 24.

2-[3-[[4-[3-[Benzyl[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]phenoxy]benzoic acid

NMR ($CDCl_3$, δ): 1.96 (2H, quintet, J=7Hz), 2.35-3.00 (6H, m), 3.86 (1H, d, J=13Hz), 3.89 (1H, d, J=13Hz), 4.66 (1H, dd, J=10, 3Hz), 6.80-8.10 (21H, m)

(+)ESI-MS (m/z): 656 $(M+H)^+$

Example 49

The following compound was obtained according to a similar manner to that of Preparation 33 starting from the object compound of Example 35-(1).

2-[3-[[4-[3-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]benzoic acid

NMR (DMSO-d_6, δ): 1.28 (9H, s), 1.60-1.88 (2H, m), 2.58 (2H, t, J=7Hz), 2.98-3.44 (4H, m), 4.72 (1H, m), 5.56 (1H, br s, OH), 7.05-8.00 (16H, m)

(-)ESI-MS (m/z): 664 $(M-H)^-$

Example 50

The following compound was obtained according to a similar manner to that of Preparation 33 starting from the object compound of Example 9-(7).

2-[3-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-phenoxy]nicotinic acid

NMR (DMSO-d_6, δ): 1.08, 1.21 (total 9H, a pair of s), 2.65-3.00 (2H, m), 3.00-3.60 (4H, m), 4.73 (1H, m), 5.59 (1H, br s, OH), 7.10-8.00 (13H, m), 8.20-8.40 (2H, m)

(-)ESI-MS (m/z): 651 $(M-H)^-$

Example 51

The following compound was obtained according to a similar manner to that of Preparation 33 starting from the object compound of Example 35-(3).

2-[4-[[4-[2-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-

phenoxy]nicotinic acid

NMR (DMSO-d_6, δ): 1.09, 1.21 (total 9H, a pair of s), 2.65-3.00 (2H, m), 3.00-3.55 (4H, m), 4.75 (1H, m), 5.59 (1H, br s, OH), 7.10-7.60 (9H, m), 7.89 (2H, d, J=8Hz), 7.96 (2H, d, J=8Hz), 8.20-8.40 (2H, m)

(-)ESI-MS (m/z): 651 $(M-H)^-$

Example 52

The following compound was obtained according to a similar manner to that of Preparation 33 starting from the object compound of Example 35-(4).

2-[3-[[4-[3-[(tert-Butoxycarbonyl)[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenyl]sulfonyl]-phenoxy]nicotinic acid

NMR (DMSO-d_6, δ): 1.25, 1.28 (total 9H, a pair of s), 1.74 (2H, quintet, J=7Hz), 2.48-2.70 (2H, m), 2.95-3.55 (4H, m), 4.71 (1H, m), 5.56 (1H, br s, OH), 7.10-8.00 (13H, m), 8.15-8.40 (2H, m)

(-)ESI-MS (m/z): 665 $(M-H)^-$

Example 53

The following compound was obtained according to a similar manner to that of Preparation 34 starting from the object compound of Example 17.

Ethyl (R)-3'-[[4-[2-[benzyl[2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenyl]sulfonyl]-1,1'-biphenyl-2-carboxylate

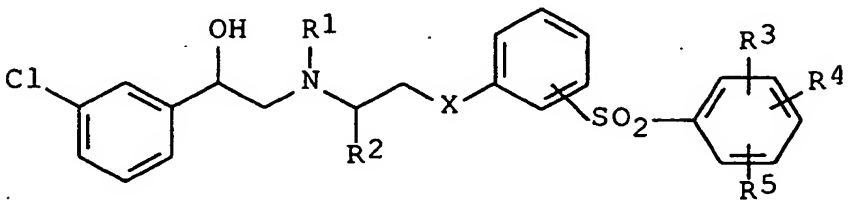
NMR ($CDCl_3$, δ): 0.85 (3H, t, J=7.1Hz), 2.5-2.9 (6H, m), 3.55 (1H, d, J=13.4Hz), 3.85-4.0 (3H, m), 4.62 (1H, dd, J=3.7, 9.9Hz), 7.15-7.35 (12H, m), 7.4-7.6 (4H, m), 7.8-7.95 (5H, m)

(+)ESI-MS (m/z): 654, 656 $(M+H)^+$

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula [I]:



[I]

wherein

X is bond, $-CH_2-$ or $-O-$,

R^1 is hydrogen or an amino protective group,

R^2 is hydrogen or lower alkyl,

R^3 is hydrogen or carboxy,

R^4 is hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy, and

R^5 is hydrogen; halogen; hydroxy;
phenyl optionally substituted with carboxy or lower alkoxycarbonyl; lower alkoxy optionally substituted with carboxy or lower alkoxycarbonyl; lower alkyl optionally substituted with carboxy or lower alkoxycarbonyl; carboxy;
lower alkoxycarbonyl;
mono(or di or tri)halo(lower)alkylsulfonyloxy;
phenoxy substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl; or pyridyloxy optionally substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl,

provided that when X is bond or $-CH_2-$, then

(1) R^5 is mono(or di or tri)halo(lower)-alkylsulfonyloxy; phenoxy substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl; or pyridyloxy optionally substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl, or

(2) R^4 is hydroxy, and R^5 is halogen; hydroxy;

phenyl optionally substituted with carboxy or lower alkoxycarbonyl; lower alkoxy optionally substituted with carboxy or lower alkoxycarbonyl; lower alkyl optionally substituted with carboxy or lower alkoxycarbonyl; carboxy; or lower alkoxycarbonyl,

or a salt thereof.

2. A compound of claim 1, wherein

X is bond, $-CH_2-$ or $-O-$,

R^1 is hydrogen,

R^2 is hydrogen or lower alkyl,

R^3 is hydrogen,

R^4 is hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy, and

R^5 is hydrogen; halogen; hydroxy;
phenyl optionally substituted with carboxy or lower alkoxycarbonyl; lower alkoxy optionally substituted with carboxy or lower alkoxycarbonyl; lower alkyl optionally substituted with carboxy or lower alkoxycarbonyl; carboxy; lower alkoxycarbonyl;
mono(or di or tri)halo(lower)alkylsulfonyloxy;
phenoxy substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl; or pyridyloxy optionally substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl,

provided that when X is bond or $-CH_2-$, then

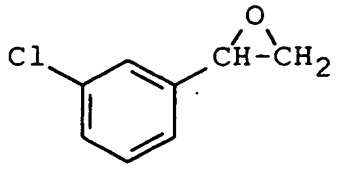
(1) R^5 is phenoxy substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl, or

(2) R^4 is hydroxy, and R^5 is carboxy or lower alkoxycarbonyl.

3. A process for preparing a compound of claim 1, or a salt thereof,

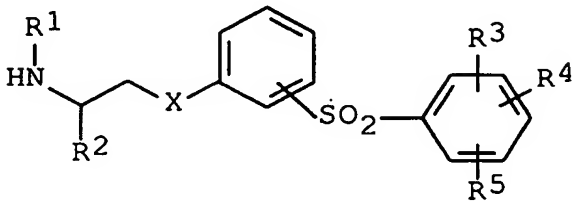
which comprises,

(i) reacting a compound [II] of the formula:



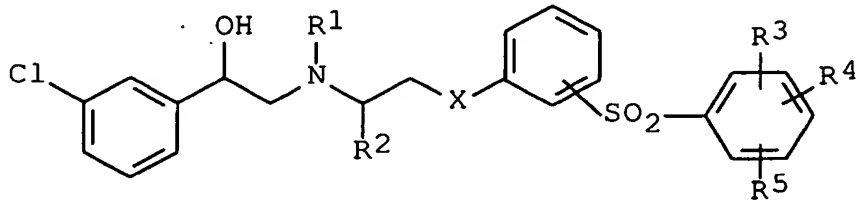
[II]

with a compound [III] of the formula:



[III]

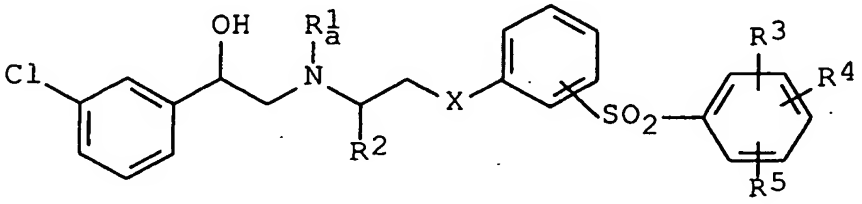
wherein X, R^1, R^2, R^3, R^4 and R^5 are each as defined in claim 1,
or a salt thereof, to give a compound [I] of the formula:



[I]

wherein X, R^1, R^2, R^3, R^4 and R^5 are each as defined in claim 1,
or a salt thereof,

(ii) subjecting a compound [Ia] of the formula :

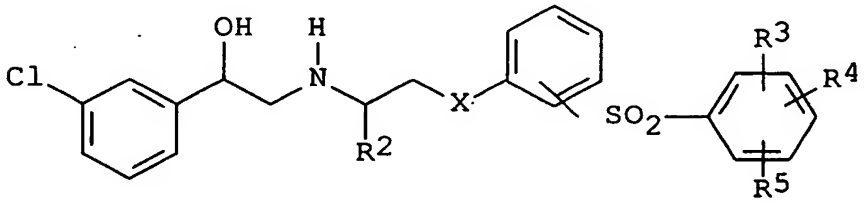


[Ia]

wherein X, R^2, R^3, R^4 and R^5 are each as defined in claim 1, and

R^1_a is an amino protective group,

or a salt thereof, to elimination reaction of the amino protective group, to give a compound [Ib] of the formula:

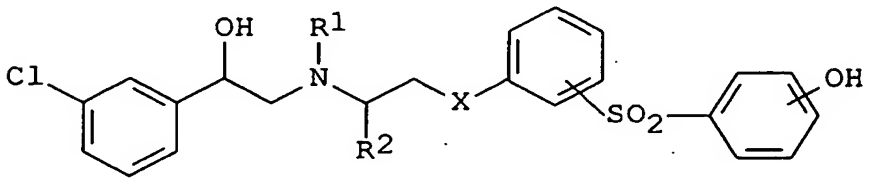


[Ib]

wherein X, R^2, R^3, R^4 and R^5 are each as defined in claim 1,

or a salt thereof, and

(iii) reacting a compound [Ic] of the formula:



[Ic]

wherein X, R^1 and R^2 are each as defined in claim 1,

or a salt thereof with a compound [IV] of the formula:

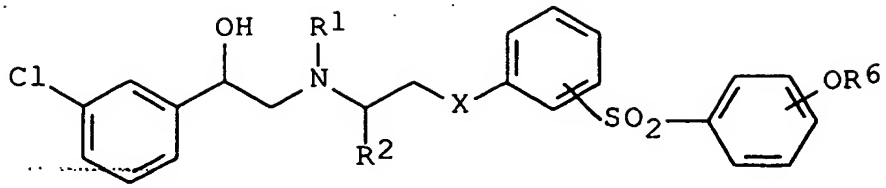
$$Y\text{-}R^6 \qquad [IV]$$

wherein R^6 is phenyl substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl; or pyridyl optionally substituted with lower alkanoyl, carboxy or lower alkoxycarbonyl, and

Y is halogen,

or a salt thereof to give a compound [Id] of the

formula:



[Id]

wherein X, R^1, R^2 and R^6 are each as defined in claim 1, and

R^6 is as defined above,

or a salt thereof.

4. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

5. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

6. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

7. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as selective β_3 adrenergic receptor agonists.

8. A method for the prophylactic and/or the therapeutic treatment of pollakiuria or urinary incontinence which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

DATED this 21st day of November, 2002
Fujisawa Pharmaceutical Co., Ltd.
By DAVIES COLLISON CAVE
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